16.1.1 Protocol and Protocol Amendments

The latest version of the Study E2609-G000-301 protocol and all previous versions are provided on the following pages:

- V8.0 23 May 2019 (Amendment 07)
- V7.0 21 Jan 2019 (Amendment 06)
- V6.0 19 Jul 2018 (Amendment 05)
- V5.0 28 Jun 2017 (Amendment 04)
- V4.0 04 Apr 2017 (Amendment 03)
- V3.0 06 Feb 2017 (Amendment 02)
- V2.0 16 Nov 2016 (Amendment 01)
- V1.0 26 Aug 2016 (original protocol)

The latest version of the Study E2609-G000-302 protocol and all previous versions are provided on the following pages:

- V7.0 23 May 2019 (Amendment 06)
- V6.0 21 Jan 2019 (Amendment 05)
- V5.0 19 Jul 2018 (Amendment 04)
- V4.0 28 Jun 2017 (Amendment 03)
- V3.0 04 Apr 2017 (Amendment 02)
- V2.0 06 Feb 2017 (Amendment 01)
- V1.0 16 Nov 2016 (original protocol)

REVISION HISTORY

Revisions to Version 7.0

New version/date: Version 8.0/23 May 2019 (per Amendment 07)

Change	Rationale	Affected Protocol Sections
Added that subjects in Japan who lose the capacity to provide informed consent during the Core Study may be eligible for inclusion in the Extension Phase if the investigators obtain subject assent and consent of the legal representative	To comply with applicable professional standards and local laws/regulations	Synopsis • Inclusion Criteria – Extension Phase Section 5.3 Appendix 5 in Section 12

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Added details for the open-label Extension Phase	As indicated in the original protocol the Extension Phase details are included	Synopsis • Study Period and Phase of Development • Study Design • Objectives • Study Treatments • Inclusion Criteria • Duration of Treatment • Concomitant Drug/ Therapy • Assessments • Bioanalytical Methods • Statistical Methods Section 5.3 Section 9.1 Figure 1 Section 9.1.3 Section 9.1.3.1 Section 9.1.4 Table 5 Appendix 5 in Section 12
Pooling of study 301 and 302	Sample size re-estimation	Synopsis

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
analysis, with decreased subjects and sites in each study	indicated the requirement for 1900 subjects compared with the original 1330 subjects per study. Studies will be combined to achieve the required numbers.	• Site(s) • Core Study Objectives • Study Design • Number of Subjects • Statistical Methods Section 6 Section 8.1 Section 8.2 Section 9.1 Section 9.2.1 Section 9.3 Section 9.7.1.1 Section 9.7.2
Study 202 summary of safety and efficacy added and its Extension Phase exposure	Emerging clinical data indicating acceptable safety and signals of clinical efficacy	Section 7.1 Section 9.4.4
Key secondary objectives defined	Three key secondary objectives have been defined from the multiple secondary objectives, indicating those of most importance that will be tested in a hierarchical manner if the primary objective is significant.	Synopsis • Core Study Objectives • Statistical Methods Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added Alzheimer's Disease Composite Score (ADCOMS) as a secondary objective for the Core Study	This novel endpoint has been included, aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change	Synopsis • Core Study Objectives, • Assessments • Study Endpoints Section 8.2 Section 9.2.1 Section 9.2.3 Section 9.5.1.3.1 Section 9.7.1.1.2 Section 9.7.1.6.2
Added of CDR-SB and ADCOMS enriched by baseline amyloid PET SUVR as a secondary objective for the Core Study	Elenbecestat may be more effective when amyloid reaches a minimum level but before too much is on board	Synopsis • Core Study Objectives, • Study Endpoints Section 8.2 Section 9.7.1.1.2

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
		Section 9.7.1.6.2
Added a biomarker objective and endpoints for the Core Study	Clarification	Synopsis • Core Study Objectives, • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 8.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Revised country list	To reflect that South Africa is a participating country	Synopsis • Study Design Section 9.1
Added that if subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator	To clarify that subjects would not need to withdraw from study	Synopsis • Study Design Section 9.1.2.1 Section 9.5.1.5.7
Added that CSF will be used to assess PD, PK, and exploratory biomarkers.	Clarification	Synopsis • Study Design Section 9.1.2.1
Added that CSF and PET assessments should be conducted before any other visit assessments and while the study is still study drug	Clarification	Synopsis • Study Design Section 9.1.2 Section 9.1.2.1
Added that new AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation	Clarification	Synopsis • Study Design Section 9.3.3
Historical cerebrospinal fluid (CSF) samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity	Allows historical CSF sample to be analyzed to determine eligibility	Synopsis • Inclusion Criteria • Assessments Section 9.3.1

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Added that levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid analysis, if available in region	For flexibility on Vitamin B12 deficiency analysis	Synopsis • Exclusion Criteria Section 9.3.2 Table 3 Section 9.5.2.2 Table 6
Revised exclusion criterion (#14) regarding a prolonged QTc interval calculated using Fridericia's formula (QTcF) was changed to clarify that if the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed.	Machine read QTcF values might be lower than central reads. Subjects are SF if the average of 3 ECGs on central read > 450 ms. Instructing sites to perform triplicate ECGs when machine reads are > 440 ms will ensure all required evaluations are completed.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.6 Table 5
Revised exclusion criterion (#19) to clarify that subjects who participated in a clinical study that involved a new chemical entity or investigational drug for Alzheimer's Disease (AD) are to be excluded	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
Added events of possible abuse potential to the safety assessments for the Core Study and Extension Phase	Clarification	Synopsis • Assessments Section 9.7.1.8
Revised text to clarify that if a Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice during the Treatment Period, that is confirmed on repeat testing and within a 6-month period, then the subject should be discontinued permanently from the study drug in the Core Study.	To clarify that this applies to Treatment Period in the Core Study.	Synopsis • Assessments Section 9.3.3
Added timepoints when the NPI-10 item will be conducted in the Extension Phase	Wording added	Synopsis • Assessments
Clarified that *ApoE4* status may be	Clarification	Synopsis

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
included in the model if appropriate		• Efficacy Analyses Section 9.7.1.6.1 Section 9.7.1.6.2
Revised Core Study analysis of biomarker endpoints to clarify that change from baseline in functional magnetic resonance imaging (fMRI) parameters as appropriate, will be determined	Clarification	Synopsis • Analyses for Biomarker Endpoints Section 9.7.1.7.3
Added that a futility analysis is planned when approximately 30% of subjects have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date	Clarification	Synopsis • Interim Analyses Section 9.7.3
Clarified that subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will need to provide separate Extension Phase-specific written informed consent	Clarification	Section 5
Added a valid period for assessment results of Tiers 1 to 5	Clarification	Section 9.1.1.1
Added information to permanent discontinuation	Clarification to cover subjects where the study drug had been temporary suspended for more than 3 weeks	Section 9.3.3
Added that termination of therapy for symptomatic treatment of AD during the study should be undertaken in compliance with local standard of care.	Clarification	Section 9.4.7
Added information on CSF sampling at Visit 13 (early discontinuation [ED])	Clarification to avoid samples being taken when subject has been off the study drug for more than 7 days.	Section 9.5.1.3.3
Revised to clarify that postdose pharmacokinetic (PK) samples will not be needed for subjects who are temporary suspended from study	To clarify requirements for collection of PK samples when subjects are not being dosed.	Section 9.5.1.4.1

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
drug or permanently stopped the study drug at the ED Visit		
Added neurogranin as an Exploratory Biomarker Subset	Correction	Table 2
Added details as to when amyloid positron emission tomography (PET) and tau PET imaging will be conducted	Clarification	Section 9.5.1.4.2
Added how adverse events (AEs) will be handled for subjects who permanently discontinue study drug, but continue in the study.	Wording added	Section 9.3.3 Section 9.5.1.5.1
Added treatment changes in depigmentation/hypopigmentation/ vitiligo/loss of hair color to the list of AEs that will require the collection of information to provide detailed description of the event	AE of interest added	Section 9.5.1.5.1
Revised blood sampling for immunological assessments and added corresponding footnote	Based on Data Safety Monitoring Board recommendation	Table 5 Table 6
Revised the example of the locally approved amyloid-imaging agent to Neuraceq	To reflect main imaging agent in use during the study	Table 4 Table 5
Added a footnote to state that Visit 2 bottles of study drug will be redispensed at Visit 3	Clarification	Table 5
Added footnotes to state when initiation, termination or change in dose is permitted and that herbal medications and preparations should be discussed with the medical monitor	Clarification	Listing 4 in Section 12
Revised list of permitted medication and permitted medication if used for short-term basis	Clarification	Listing 5 in Section 12

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Added footnote that herbal medications or preparations should be discussed with the medical monitor and benzodiazepines were deleted	Clarification	Listing 5 and Listing 6 in Section 12
An editorial revision was made to remove "(E2609)"; grammatical, typographical, and formatting changes were also made	Correction	Throughout

Revisions to Version 5.0

New version/date: Version 6.0/19 Jul 2018 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) that have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 4 Table 5 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 Table 5
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 Table 4 and Table 5
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 Table 5
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis • Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Core Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 Table 5
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection is exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or ECG at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 5) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis • Bioanalytical Methods • Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 Table 4
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 Table 5

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 Table 2
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 Table 4
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 Table 6
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result	Added for clarification	Section 11.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
documentation from the urine dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted “pharmacogenomics (PGx)” data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4 (new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSF collection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4 and Table 5)
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the medical monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.5
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14)	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 3) Section 9.5.2.1(Table 4 and Table 5)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for pharmacokinetic analysis during the treatment and follow-up periods; added specimen collection for coagulation; added clarification that the volumes are estimates and may vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 6
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 3 Section9.5.2.1, Table 4

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 4), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification to the exclusion criteria for absolute	Clarification to explain the standardized method of ALC	Synopsis • Exclusion Criteria

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	calculation used across sites	• Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 5
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the Treatment Period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.2.1 Section 9.5.2.1 (Table 4 and Table 5)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 5)
Blood volumes for PK, pharmacodynamic (PD), and	Corrected to align with the Schedule of Procedures/	Section 9.5.2.2, Table 6

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
exploratory biomarkers were revised	Assessments	
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs with symptomatic effects.	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made mandatory at the second of the follow-up visits.	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 5
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 3 Table 4 Table 5

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	DSMB for periodic review during the study	Table 6
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as secondary	Section 9.2.1
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat (E2609)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02) V4.0 04 Apr 2017 (Amendment 03) V5.0 28 Jun 2017 (Amendment 04) V6.0 19 Jul 2018 (Amendment 05) V7.0 21 Jan 2019 (Amendment 06) V8.0 23 May 2019 (Amendment 07)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements forPharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing

this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Approximately 250 global sites (revised per Amendment 06)

Study Period and Phase of Development

This Phase 3 study will consist of:

- Core Study: The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up
- Open-label Extension Phase: Up to 24 months of additional treatment, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first, and 1-month follow up. (revised per Amendment 06)

Core Study Objectives

Primary Objective

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD) pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 06)

Key Secondary Objectives (revised per Amendment 06)

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-301

Other Secondary Objectives (revised per Amendment 06)

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET standardized uptake

value ratio (SUVR) pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale - cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE) and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] amyloid beta [Aβ] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 06)
- To explore potential plasma and CSF biomarkers of Alzheimer's disease (AD)

(eg, neurofilament [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 [YKL-40], and neurogranin [Ng]) (revised per Amendment 06)

- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

Exploratory Objectives

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Extension Phase Objectives (revised per Amendment 06)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with EAD

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on CDR-SB, ADCOMS, MMSE, FAQ,ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia, for subjects who were not clinically staged as having dementia at Core Study baseline, based on a clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is

maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by PET (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using vMRI
- To evaluate the long term-effect of elenbecestat in preserving brain connectivity as measured by task-free fMRI
- To evaluate the long-term effect of elenbecestat on CSF tau, p-tau, and Aβ levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, Ng)

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other AD pharmacotherapies
- To explore the long-term effect of elenbecestat on the NPI-10 and if available NPI-12

Study Design

The study consists of a Core Study followed by an open-label Extension Phase. The Core study is a 24-month treatment with a 3-month follow up, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 06)

Study E2609-G000-301 and Study E2609-G000-302 will be combined with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 06)

In this Core Study, subjects will be randomized in a double-blind manner to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01, 02, and 06)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET, tau PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. (revised per Amendments 05 and 06)

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. . The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 03 and 06).

Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 05) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, ISLT, and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains

unchanged throughout the study. (revised per Amendment 04)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01, 02, and 04) Vital signs and weight will be recorded, and a single 12-lead ECG will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities that may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task-free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both. (revised per Amendment 04) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies, respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment

Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. Inclusion and exclusion criteria will be reviewed again, together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 02 and 05)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

In some cases, unscheduled (UNS) visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and is not within 3 months of a previous CSF sample). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug (revised per Amendment 05 and 06)

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24-month Treatment Period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study

investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 04) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 06) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 06)

Extension Phase

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

During the Extension Phase, the assessment of safety will include the recording of all AEs. In addition, vital signs, weight, safety blood and urine laboratory tests, ECGs [no central reading of ECGs], suicidality, neurological examination, NPI, and signals of abuse potential will continue to be assessed.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study) and at Visit 24/ED, but will be abbreviated for all other timepoints.

Clinical assessments will be performed every 4 months (MMSE, FAQ) or 12 months (CDR, ADAS-cog14). Blood biomarkers and MRI will be assessed every 12 months. Optional amyloid and tau PET and CSF biomarker assessments will be conducted at the end of 2-year open-label treatment (Extension Phase).

Subjects who complete treatment in the Extension Phase or who discontinue the study drug are required to complete the Follow-up Visit, 1 month after the last dose.

Subjects may discontinue from the open-label study drug for any reason, but will be required to complete the ED Visit (within 7 days of last dose) and the Follow-up Visit 1 month after the last dose of study drug. In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3, are met. (revised per Amendment 06)

Number of Subjects

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 06)

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or mild AD disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau:Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility, but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 04 and 06).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications that are administered as short courses (eg, up to 3 weeks unless discussed and agreed with medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

Extension Phase (revised per Amendment 06)

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 07)
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

Core Study

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:

- total abstinence (if it is their preferred and usual lifestyle)
- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 04 and 06)
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or

C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during Screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below LLN or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 06)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 04)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection. (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid

treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 06)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo. (revised per Amendment 06)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Extension Phase

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food. (revised per Amendment 06)

Duration of Treatment

Core Study: The maximum estimated duration for each subject is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow up).

Extension Phase: The estimated duration for a subject is 25 months (ie, 24 months of treatment and 1-month follow up). (revised per Amendment 06).

Concomitant Drug/Therapy (both Core Study and Extension Phase)

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 02)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 02 and 04)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 03 and 06) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis

and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 04 and 06)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments (both Core Study and Extension Phase)

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD. ADCOMS (Wang, et al., 2016) is a composite clinical score that represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, of the MMSE, the CDR, and the ADAS-cog14. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change. (revised per Amendment 06)

Pharmacokinetic Assessments (Core Study Only)

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (both Core Study and Extension Phase)

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, 03, and 04)

Blood will be collected to measure PD and biomarkers in both the Core Study and the Extension Phase. (revised per Amendments 02, 03, 04, and 06)

Amyloid PET imaging or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 04) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor), but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. Historical CSF samples

may be analyzed to confirm amyloid pathology, if collected, processed, and stored under appropriate conditions and approved by the sponsor. (revised per Amendments 04 and 06)

Subjects who consent to participate in the amyloid and tau-PET longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED Visit in the Core Study and at 24 months or at the ED Visit in the Extension Phase. (revised per Amendments 04, 05, and 06)

Subjects who consent to the CSF substudy will have samples taken at 24 months or at the ED Visit in both the Core Study and Extension Phase for PD and biomarker assessments. (revised per Amendment 06)

Safety Assessments (both Core Study and Extension Phase)

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings (evaluated by a central reader in the Core Study); physical, dermatologic, and neurologic examinations; assessment of suicidality, events of possible signals of drug abuse potential, and MRIs during the Treatment Period. (revised per Amendments 01 and 06)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when ALC returns to greater than 800/mm3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6-month period during the Core Study treatment, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period, then the subject should be discontinued permanently from the study drug. (revised per Amendments 01, 02, 04, and 06)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly until Month 3 of treatment in the Core Study and until Month 2 in the Extension Phase. Thereafter, they will be monitored every 3 months in the Core Study and every 4 months in the Extension Phase until the end of the Treatment Period and at Follow-up Visits. (revised per Amendment 06)

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be

performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period or during the first 4 weeks of the Follow-up Period in the Core Study and during the Extension Phase will require a more detailed follow up. (revised per Amendments 04 and 06)

Other Assessments (Core Study Only)

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Other Assessments (Extension Phase Only)

The NPI-10 or if available NPI-12 will be conducted at Day 1, Month 4, Month 12, and then every 12 months. If the NPI-12 questionnaire is used, both NPI-10 and NPI-12 scores will be generated. (revised per Amendment 06)

Bioanalytical Methods (both Core Study and Extension Phase)

CSF AD assessment (eg, tau:Aβ(1-42) ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits (revised per Amendment 04) Exploratory biomarkers such as neurofilament NFL, Ng, YKL-40, and VILIP1 may also be measured using validated assays. (revised per Amendments 02 and 06)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 04)

Plasma concentrations of elenbecestat that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 06)

Core Study
Study Endpoints
Primary Endpoint

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 06)

Key Secondary Endpoints (revised per Amendment 06)

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the

combined studies

- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

Other Secondary Endpoints (revised per Amendment 06)

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies (revised per Amendment 01)
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies (revised per Amendment 01)
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in plasma amyloid biomarker eg, Aβ(1-x) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng (revised per Amendment 06)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and

subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 02, and 06) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple

imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendments 01 and 06)

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 06)

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 06)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. *ApoE4* status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 04, 05, and 06)

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 06)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on

change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha=0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendments 01 and 06)

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the

whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Extension Phase (revised per Amendment 06)

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42)) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

Extension Phase Analysis Sets

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, FAS, PPS, and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at

Core Study baseline based on clinical diagnosis

- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive an increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al., 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, the MMRM model will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET SUVR
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change in baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline in Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints. The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at the time of the futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 06)

Sample Size Rationale

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by

the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 06)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCOMS	Alzheimer's Disease Composite Score
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating –Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system

Abbreviation	Term
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	early Alzheimer's disease
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)

Abbreviation	Term
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau

Abbreviation	Term
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SUVR	standardized uptake value ratio
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 04) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 04)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative or study partner). (revised per Amendment 04) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 05)

Subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will be asked to provide separate Extension Phase-specific written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (as determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 07)

At the start of the Extension Phase, an assessment of capacity to consent should be undertaken, and continue periodically throughout the Extension Phase treatment, utilizing the method and frequency as for the Core Study above. (revised per Amendment 06)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 250 investigational sites globally. (revised per Amendment 06)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ-secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat Investigator's Brochure). Another study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat was administered orally by gavage once a day to male rats for 28 days before, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 04) Further details of the nonclinical data to date with elenbecestat can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing to assess the PK levels of elenbecestat and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open-label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat. It also investigated the effects of elenbecestat on the PK properties of digoxin. (revised per Amendment 04)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open-label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open-label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat. (revised per Amendment 02)

Study E2609-G000-202 (Study 202) has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat given daily, along with safety and exploratory efficacy. Elenbecestat was generally well tolerated; no unexpected safety concerns emerged. Although sample sizes were small, statistically significant decreases in PET standardized uptake value ratios (SUVR) were seen. Clinical assessments suggest elenbecestat may have attenuating effects on cognitive decline in MCI-to-moderate AD subjects (Lynch, et al., 2018). Forty-three out of the 70 randomized subjects completed the study and of these 41 elected to enroll in an open-label Extension Phase. The Extension Phase has been running for 2 years and currently has 36 subjects still receiving elenbecestat. (revised per Amendment 06)

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat. In elderly subjects treated with 50 mg of elenbecestat, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects who were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or ECG parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of

latent infections in subjects who received single doses of elenbecestat. A single dose of elenbecestat up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat when coadministered with elenbecestat but not when dosed at least 2 hours apart from elenbecestat. Elenbecestat (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat. Based on these results, it is not considered necessary to impose restrictions during elenbecestat treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications that are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when elenbecestat will not be present, as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study

confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T-wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat. The effects of elenbecestat on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50-mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat PK parameters (C_{max} and AUC). (revised per Amendment 04) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the Core Study is:

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 06)

8.2 Secondary Objectives

The key secondary objectives of the Core Study are as follows (revised per Amendment 06):

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-301

The other secondary objectives of the Core Study are as follows (revised per Amendment 06):

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of CDR scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline

based on a clinical diagnosis evaluated every 3 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale - cognitive subscale14 ($ADAS\text{-}cog_{14}$), Mini Mental State Examination (MMSE) and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF total tau [t-tau] amyloid beta [Aβ] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], and functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the population PK of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 06)
- To explore potential plasma and CSF biomarkers of AD (eg, neurofilament [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 [YKL-40], and neuroganin [Ng]) (revised per Amendment 06)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)

- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD, as deemed appropriate To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

8.3 Exploratory Objectives

The exploratory objectives of the Core Study are:

- To explore the relationship between elenbecestat exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

For objectives specific to the Extension Phase, refer to Appendix 5 in Section 12.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group Core Study with an open-label Extension Phase in EAD including MCI due to AD (Albert et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow-up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 06)

Study E2609-G000-301 and Study E2609-G000-302 will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study.

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01, 02, and 06)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. (revised per Amendments 05 and 06)

The maximum estimated duration for each subject in the Core Study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow-up).

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days, (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase. (revised per Amendment 06)

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified

to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. (revised per Amendment 06) The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

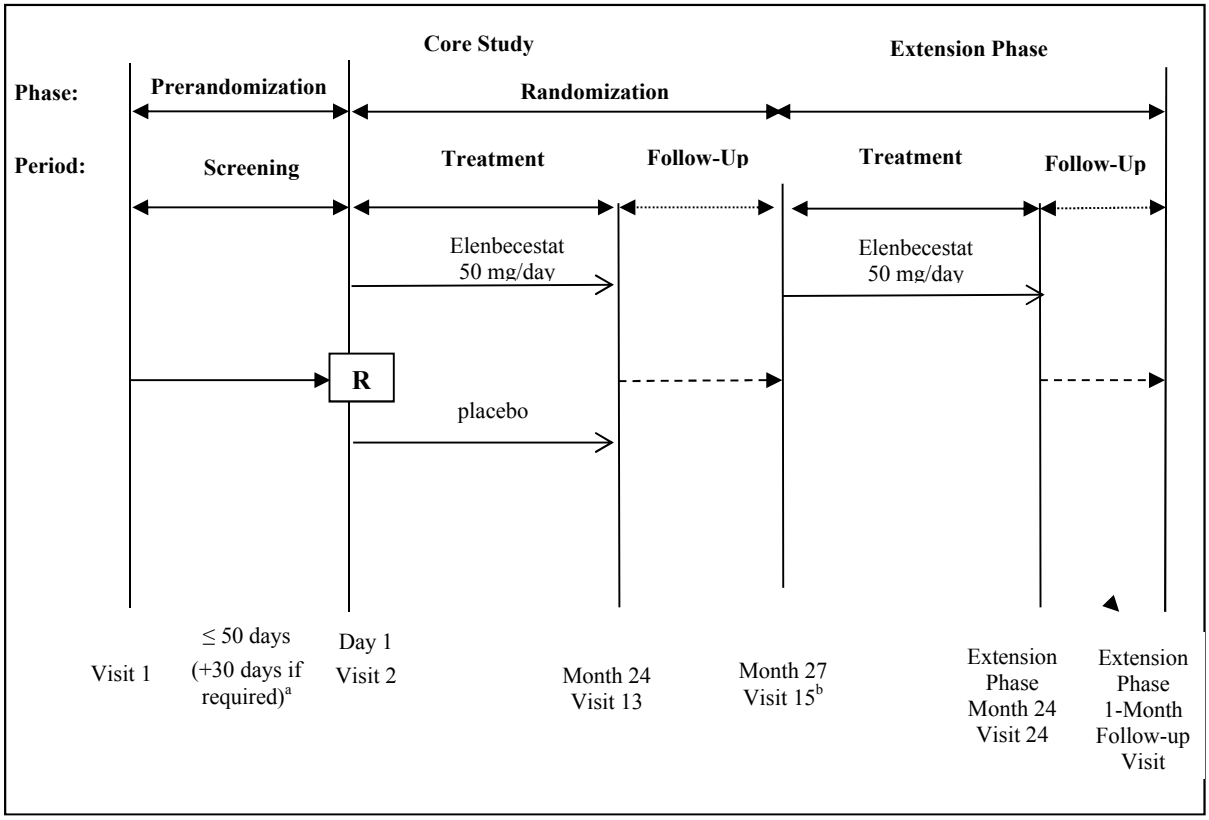

Figure 1 Study Design for E2609-G000-301 (revised per Amendment 06)

Elenbecestat = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a: Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

b: The last day of the Core Study (Visit 15) is also the first day of the Extension Phase

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained before the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5 (ie, during the Randomization Phase of the study). Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie, during the Randomization Phase of the study). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02, 04, and 05)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of Screening. (revised per Amendment 05)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Subjects may be re-screened, if deemed appropriate by the investigator and medical monitor. Unless otherwise stated, results of the following will be valid over the timeframes stated below (revised per Amendment 06):

- Tiers 1 to 3 Screening will be valid for 96 days from the date of assessment.
- Tier 4 MRIs will be valid for 90 days from the date of assessment.
- Tier 5 CSF results and amyloid PET scans will be valid for 90 days from the date of assessment, while historical amyloid PET scans will be valid for 12 months.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, ISLT, CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, before the CDR is administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 04)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart

rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs), which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 03 and 04) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities that may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment, or both. (revised per Amendment 04) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for lumbar puncture (LP) to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 04) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). The tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before

randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies, respectively. (revised per Amendment 04) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the LP. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of assessment for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 04) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05).

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 04 and 05).

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal

CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 02, 04, and 05) CSF and PET assessments should be conducted before any other visit assessments and while the subject is still on study drug. (revised per Amendment 06) Refer to Table 5 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04) Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED Visit/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD, and assessment of immune status are performed at different intervals throughout the Treatment Period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug. (revised per Amendments 02, 04, 05, and 06) Please refer to Schedule of Assessments (Table 5).

In some cases, unscheduled (UNS) visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-up Period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment on study drug and the 3-month follow up in the Core Study. The open-label Extension Phase will continue for 24 months, or until commercial availability of elenbecestat, or until a positive benefit-risk assessment in this indication is not demonstrated, whichever comes first (See Appendix 5 for full details of the Extension Phase). (revised per Amendments 03 and 06)

9.1.3.1 Extension Phase Follow-Up Period (revised per Amendment 06)

All subjects, regardless of whether they complete all 24 months of open-label treatment or discontinue study drug prematurely, will complete a post-treatment Follow-up Visit 1 month after the last dose of open-label study drug.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments in Appendix 5) will depend on the reason for the UNS visit and will be decided at the discretion of the investigator.

9.1.4 End of Study

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 03 and 06)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

Study E2609-G000-301 and Study E2609-G000-302 are multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group studies in subjects with EAD including MCI due to AD and the early stages of mild AD. The 2 studies will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study across 2 treatment groups, (placebo, 50 mg per day elenbecestat) for 24 months. (revised per Amendment 06) The maximum estimated duration for each subject on study is

anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month Follow-up Period).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment, and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog14 (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. A novel composite endpoint, ADCOMS (Wang, et al., 2016), is also included as a secondary endpoint. (revised per Amendments 01 and 06)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 04)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes

(eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). Therefore, attempts to slow disease progression with elenbecestat are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog14 immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical

meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

ADCOMS is a weighted linear combination of 12 items from 3 of the above clinical scales, the ADAS-cog, the MMSE, and the CDR. These 12 items consist of the predictive variables A4, A7, A8, A11, M1, M7, C1, C2, C3, C4, C5, and C6. The names of these items and the corresponding scale names are described in Table 1. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.

Table 1 Predictive Variables for the ADCOMS

Scale	Item ID	Item Name	PLS weight
ADAS-cog	A4	Delayed Word Recall	0.00847483
	A7	Orientation	0.017088
	A8	Word Recognition	0.003732761
	A11	Word Finding	0.016211
MMSE	M1	Orientation Time	0.041567
	M7	Drawing	0.038238
CDR	C1	Personal Care	0.054321
	C2	Community Affairs	0.1091
	C3	Home and Hobbies	0.089039
	C4	Judgment and Problem Solving	0.069493
	C5	Memory	0.058724
	C6	Orientation	0.078152

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale, CDR = Clinical Dementia Rating, ID = identification, MMSE = Mini Mental State Examination, PLS = Partial Least Squares.

(revised per Amendment 06)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat treatment.

9.2.4 Rationale for Biomarkers

CSF biomarkers, amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a LP procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 05)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ[1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendments 01 and 04)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 04) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 05)

Tau PET imaging will be performed to evaluate the effects of elenbecestat on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who

have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason, hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as NFL, Ng, VILIP1, or YKL-40) become available. (revised per Amendments 02, 03, and 06)

9.3 Selection of Study Population

At least 850 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 250 centers worldwide (revised per Amendment 06). Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau: Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 04 and 06).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per

Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

For inclusion criteria specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age

group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 04 and 06)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during Screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 06)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 04)

    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

NOTE: The following subjects do not need to be excluded:

- Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety. (revised per Amendment 04)
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTcF interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 06)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 06)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery that requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when ALC returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments (Table 5) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing occurs twice within a 6-month period during the Core Study, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period then the subject should be discontinued permanently from study drug. (revised per Amendments 01, 02, 04, and 06)

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 02 and 03) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 03)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 03)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 03)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study

drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

For subjects who temporarily suspend study drug (eg, ALC <800/mm^3) but progress to permanently discontinue study drug, the ED and Follow-up Visits should be scheduled as follows: (revised per Amendment 06)

- If ≥3 weeks from the last dose, then the ED Visit should be scheduled immediately, and the 1 month Follow-up Visit will not be required
- If <3 weeks from the last dose, then the ED Visit should be scheduled immediately, and Follow-up Visits at 1 and 3 months after the last dose will be required

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 06) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

Core Study

For this study, the test drug is elenbecestat and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 5 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the Treatment Period, the investigator should discuss with the medical monitor whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

For details on treatment to be administered in the Extension Phase, refer to Appendix 5 in Section 12.

9.4.2 Identity of Investigational Product(s)

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat

- Test drug code: E2609
- Generic name: elenbecestat
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) along with safety and exploratory efficacy of 5, 15, and 50 mg of elenbecestat given daily. Based on the PK/PD modeling results,

elenbecestat 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 03) Based on these data, elenbecestat 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 02)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 02 and 04)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 03 and 06) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 04 and 06)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable

- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 4 and Table 5. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a

clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment, and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog14: The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-cog14 that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-cog14. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0 to 10. (revised per Amendment 03)

ADCOMS: ADCOMS is a composite score of 12 items from the CDR, MMSE, and ADAS-cog, and does not require any additional assessments. (revised per Amendment 06)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 4 and Table 5, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7 to 10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available for screening to determine subject eligibility for the study. (revised per Amendment 03) Subjects who undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal.

CSF samples at Visit 13 should be collected while the subject is still on the study drug and before the other visit assessments. All ED CSF samples need to be taken no later than 7 days

after the last dose of study drug. All CSF samples should be taken at approximately the same time of day as at the Screening Visit. (revised per Amendment 06)

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to the CSF procedure at Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat. Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 04) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 4 and Table 5. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose PK samples are not required. (revised per Amendment 06)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 2 lists PD, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 04)

Table 2 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (revised per Amendment 06)

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Example of Exploratory Biomarkers	PD	Example of Exploratory Biomarkers
Whole Blood/ Plasma	*ApoE* [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) Aβ42/Aβ40 ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 Tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)
a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 03 and 04)

The plasma samples will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 03 and 04)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 4 and Table 5. (revised per Amendment 03) The blood sample collected for PD/exploratory biomarker analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 04)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the

event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 03 and 04) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 04) The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

For subjects participating in the amyloid PET substudy, amyloid PET imaging will be conducted on separate days from the scheduled visits and should be conducted before the clinic Visit 9 and no later than 7 days after the last dose for Visit 13/ED. (revised per Amendment 06)

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 05)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

For subjects participating in the tau PET substudy, tau PET imaging will be conducted on separate days from the scheduled visits and should be conducted before clinic Visit 13/ED and no later than 7 days after the last dose of study drug. (revised per Amendment 06)

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities that will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 05)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 4 and Table 5); and MRIs as detailed in Table 4 and Table 5. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 4 and Table 5. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs that will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06)

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF until 4 weeks post last dose, and followed up for 12 weeks, or until resolution, whichever comes first (as shown in Table 5). Adverse events relating to study procedures will be collected until the end of study participation. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. (revised per Amendment 06)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog14, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines), (revised per Amendment 04)

Euphoria-related terms: (revised per Amendment 04)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 04)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 04)

- Somnolence (revised per Amendment 04)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 04)

- Psychosis
- Aggression (revised per Amendment 04)
- Confusion and disorientation (revised per Amendment 04)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 04)

- Drug tolerance
- Habituation (revised per Amendment 04)

- Substance related disorders (revised per Amendment 04)

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug): (revised per Amendment 04)

- Drug withdrawal syndrome (revised per Amendment 04)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the medical monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); treatment-emergent depigmentation/hypopigmentation/vitiligo/loss of hair color; amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendments 03 and 06)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. Table 4 and Table 5 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time), and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 02 and 03). A prothrombin time and INR should also be performed before LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 (with reflex MMA if available for low vitamin B12) (revised per Amendment 06) Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs, which will be stored for testing if required. (revised per Amendments 01 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, MMA = methylmalonic acid, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 4 and Table 5 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 5. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 4 and Table 5. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 03) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 5 and will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 4 and Table 5. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendments 01 and 06)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 4 and Table 5. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

9.5.1.5.8 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 5).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 4 and Table 5, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 03) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 03) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the medical monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 5 presents the schedule of procedures/assessments for the Randomization Phase.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 04)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendment 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendment 04)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 03)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 05)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 04 and 05)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QTcF = QTc interval calculated using Fridericia's formula, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. (revised per Amendment 05)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, before the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report,

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1

(3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR, derived from the prothrombin time, and aPTT are to be performed as part of Screening. (revised per Amendments 02 and 03).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 04) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 03)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Neuraceq, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 90 days from the date of the original screening procedure. (revised per Amendments 05 and 06)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 2 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendments 05 and 06)

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Consent (subject and study partner)															X[dd]	
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X														X[dd]	
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (revised per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments (revised per Amendment 03)[ee]	X	X	X	X	X	X	X	X								
PBMCs for storage and testing required (revised per Amendment 06)	X					X		X				X	X			

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X[dd]	X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog14[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI-10	X					X		X		X		X	X		X[hh]	
C-SSRS	X	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X	X		X[dd]	
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X[ii]	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X		X[cc]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Tau PET (optional substudy)[u]												X	X		X[cc]	
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[y]												X	X		X[cc]	
Adverse events[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[b] [b]	X	X	X	X	X	X	X	X	X	X				X[dd]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																

Notes:

ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, QTcF = QTc interval calculated using Fridericia's formula, UNS = unscheduled, vMRI = volumetric MRI.

a: A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visits 7 to 13 inclusive (including for subjects who discontinue study drug early but who return for clinical assessments at 12 and 24 months). These windows should be calculated from Day 1. A window of ±3 days calculated from the last dose will be permitted for the Follow-up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS-cog14) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, only AEs relating to study procedures will be collected. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-up Visits (Visit 14 and Visit 15).

c: All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Visit 15 will also act as Baseline for subjects who successfully complete the Core Study and will be enrolled into the open-label Extension Phase. (revised per Amendments 01, 02, and 06)

d: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.e: Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15, or if the subject is continuing in the Extension Phase.

f: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

g: A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED) and Visit 15 if entering the Extension Phase (revised per Amendment 06) Neurologic examinations at the other visits will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h: Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i: Single 12-lead standard ECGs will be recorded. If the QTcF machine read is greater than 440 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values. (revised per Amendment 06)

j: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k: More frequent testing may be required per local regulations. (revised per Amendment 04) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m: Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 04)

n: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

o: Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

p: The clinical assessment of suicidality will require input from both the subject and the study partner

q: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

r: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

s: MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the medical monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t: Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuraceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 04 and 05)

u: For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 05)

v: Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w: Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, then postdose PK samples are not required.

x: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 01, 03, and 04)

y: For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 02, and 04)

z: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

aa: AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	UNS Visit[d]
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 02 and 04)

bb: The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Visit 2 bottles are re-dispensed at Visit 3 after accountability is performed. (revised per Amendment 06)

cc: Only for Extension Phase subjects who did not participate in optional longitudinal substudies in the Core Study but who wish to consent to optional longitudinal substudies in the Extension Phase

dd: For subjects entering the Extension Phase only

ee: Immunological assessments only required for subjects randomized before 07 Sep 2018

ff: New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, AEs relating to study procedures will be collected only

gg: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

hh: For those subjects entering the Extension Phase, NPI-12 will be used if available and both NPI-10 and NPI-12 scores calculated.

ii: Not required for those entering Extension Phase

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 4 and Table 5 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 4). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 6 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 03) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 03)

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 03 and 04)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 04)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 03 and 04)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 03)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 03 and 04)	1	None	1×3.5 mL	none	3.5 mL

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening and MMA where available (revised per Amendments 03, 04, and 06)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments Amendments 01, 04, and 06)[b]	8	none	1×10 mL	7×10 mL	80 mL
Blood for PBMCs (revised per Amendment 06)	4	none	1×10 mL	3×10 mL	40 mL
Blood for immune status (revised per Amendment 04)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 04)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 02, 03 and 04)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendments 02 and 03)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 02, 03, 04, and 06)		25.8 mL	46.8 mL	298.9mL	371.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit); actual volume may vary based on local regulations. (revised per Amendment 03)
b: Immunological assessment samples not required for subjects randomized after 07 Sep 2018 - reducing total blood volume to 291.5 mL (revised per Amendment 06)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 4 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. (revised per Amendment 06)

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 04)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 04)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (ocular herpes, new onset seizures, and symptomatic cerebral vasogenic edema), as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 5 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

For statistical methods specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 06)

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 06)

9.7.1.1.2 SECONDARY ENDPOINTS

The key secondary endpoints of the study are as follows (revised per Amendment 06):

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

The other secondary endpoints of the study are as follows (revised per Amendment 06):

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies (revised per Amendment 01)
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies (revised per Amendment 01)
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies (revised per Amendment 01)

9.7.1.1.3 BIOMARKER ENDPOINTS

The biomarker endpoints of the study are:

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

9.7.1.1.4 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog14, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization [Visit 2] [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 02, and 06) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model. Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendments 01 and 06)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 06):

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 06)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. ApoE4 status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Proportion of subjects with

dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 01, 04, 05, and 06) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, with treatment group and randomization stratification variables, as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06)

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$) derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)

- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 06)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendments 01 and 06)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 04)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will

be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog14, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 06)

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined two studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 06)

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during

DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter. (revised per Amendment 06)

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 02 and 04)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a] Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 04)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Initiation, termination or change in dose is permitted if in line with local standard of care. Any changes are required to be stable for 4 weeks before any cognitive assessments.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of cognitive enhancements then they should follow the same rules as the medications in this listing. (revised per Amendment 06)

Listing 5 Medications Permitted if Used on PRN or Short Term Basis (2 to 4 Weeks) Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Benzodiazepines (revised per Amendments 04 and 06)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Sedatives	
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	

PRN = Pro re nata

This list is not exhaustive.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of negative effects on cognition then they should follow the same rules as the medications in this listing. (revised per Amendment 06)

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 04)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 04)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts

Categories (revised per Amendment 04)			**Examples**[a]	
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 04)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 04)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	

Categories (revised per Amendment 04)			**Examples**[a]	
(revised per Amendment 04)	**17**	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 04)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 04)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 04)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 04)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 04) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

Appendix 5 Open-label Extension Phase (revised per Amendment 06)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on Clinical Dementia Rating –Sum Of Boxes (CDR-SB), Alzheimer's Disease Composite Score (ADCOMS), Mini Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14), and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia for subjects who were not clinically staged as having dementia at Core Study baseline, based on clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by positron emission tomography (PET) (optional substudies)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using volumetric magnetic resonance imaging (vMRI)
- To evaluate the long-term effect of elenbecestat in preserving brain connectivity as measured by task-free functional magnetic resonance imaging (fMRI)
- To evaluate the long-term effect of elenbecestat on cerebrospinal fluid (CSF) t-tau, phosphorylated-tau (p-tau), and amyloid beta (Aβ) levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL),visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin [Ng])

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other Alzheimer's disease (AD) pharmacotherapies
- To explore the long-term effect of elenbecestat on the Neuropsychiatric Inventory (NPI)-10 and if available NPI-12

Eligibility Criteria

Subjects who do not meet all of the inclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 07)
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Study Design and Plan

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 24 months (2 years), or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first.

Subjects who are enrolled and complete the Core Study, including the 3-month Follow-up Period, will have the option to participate in the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not provide consent to transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

Subjects may discontinue from the open-label study drug for any reason but are required to complete the Early Discontinuation (ED) Visit (within 7 days of last dose). In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3 (Removal of Subjects from Therapy or Assessment) are met.

Subjects who complete the 24 months of Extension Phase treatment, or discontinue the study drug are required to complete the Follow-up Visit, 1 month after their last dose. The study will end when the last subject has completed the last Extension Phase study visit.

Treatment

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food.

Assessments

Assessments will be conducted as shown in Table 5 Visit 15 (Day 1 of the Extension Phase) and as shown in Table 9, for all other Extension Phase visits following the guidelines as indicated for the Core Study in Section 9.5. Concomitant therapy is allowed as stated in Section 9.4.7 and treatment compliance and accountability will be performed as indicated in Section 9.4.8, and Section 9.4.9, respectively.

Safety assessments (physical examinations, neurological examinations, vital signs, safety laboratory tests, ECGs [no central reading of ECGs], signals of potential abuse, pregnancy test for females of child-bearing potential, Columbia Suicide Severity Rating Scale (C-SSRS), and assessment of suicidal thinking/behavior, immunological assessments, safety magnetic resonance imaging (MRI) will be monitored according to Table 9 and all adverse events (AEs) and serious adverse events (SAEs) recorded.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study), and at Visit 24/ED, but will be abbreviated for all other timepoints.

Safety laboratory blood tests will be collected as indicated in Table 9 and analyzed by a central laboratory.

Blood samples for pharmacodynamic (PD) and biomarker analyses (Table 7) will be collected as indicated in Table 9. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Subjects that have consented to the optional CSF substudy (either at the start of the Core Study or Extension Phase) will have samples taken as indicated in the Table of Assessments to analyze PD and biomarkers (Table 7). Longitudinal CSF sample is taken before other Visit 24 assessments and whilst subject is still on study drug; for ED, CSF should be taken and no longer than 7 days after the last dose.

Safety brain MRI, vMRI, and fMRI assessments will be performed at the end of the Extension Phase Treatment Period (Visit 24 or ED). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be conducted centrally. If subjects have non-MRI compatible devices fitted during the Extension Phase treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator.

Table 7 Extension Phase Samples

Sample	PD	AD Biomarkers	Example of Exploratory Biomarkers
Blood	Aβ(1-x)		Tau NFL VILIP1 YKL-40
CSF		Aβ(1-42) Tau p-tau	NFL Neurogranin VILIP1 YKL-40

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), CSF = cerebrospinal fluid, NFL = neurofilament light, VILIP1 = visinin like protein 1, YKL 40 = human cartilage glycoprotein-39

Optional amyloid and tau PET assessments will be performed at the end of the Extension Phase Treatment Period before other Visit 24/ED assessments and when subjects are still on the study drug and no more than 7 days after the last dose of study drug. Subjects may consent to participate in the PET substudies at the start of the Extension Phase, for whom an additional assessment will be conducted at Visit 15 (before the first dose of the open-label study drug). PET scan acquisition and interpretation will be conducted centrally.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the start of the Extension Phase and at the end of treatment and a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive answer to any clinical assessment of suicidality question (subject or study partner) requires the C-SSRS to be performed; any positive finding on the C-SSRS requires a psychiatric evaluation to be conducted.

Clinical assessments (MMSE, FAQ, CDR, ADAS-cog14, disease staging, NPI) will be administered as described in the Schedule of Assessments (Table 9) and a central review employed to ensure global standardization. If available the NPI version 12 (NPI-12) questionnaire will be used, but both NPI-10 and NPI-12 scores will be calculated.

The Follow-up Visit will take place at 1 month after the last dose of study drug as described in Table 9. These assessments will also be performed if a subject prematurely discontinues from the Extension Phase.

The number of blood samples and the total volume of blood that will be collected throughout the Extension Phase, are summarized in Table 8.

Table 8 Summary of Sample Volumes

Assessment	Total Number Of Collection Time Points[a]	Number Of Time Points x Volume Per Collection (mL)	Total Volume (mL)
		Extension Phase Treatment and Follow-Up Periods	
Blood			
Safety labs	11	11×6.3 mL	69.3 mL
PD & biomarker sample	3	3×6 mL	18 mL
Total volume blood collected			**87.3 mL**
CSF PD and biomarker	2[a]	2×12 mL	24 mL

CSF = cerebrospinal fluid, PD = pharmacodynamic
a: For subjects who consented to the CSF substudy in the Core Study, only 1 sample (12 mL) is required to be collected

EXTENSION PHASE STATISTICAL METHODS

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall):
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline, based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

EXTENSION PHASE ANALYSIS SETS

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, Full Analysis Set (FAS), Per Protocol Analysis Set (PPS), and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al., 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, a mixed effects model for repeated measures (MMRM) will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET standardized uptake value ratio (SUVR)
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints.

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Sample Size Rationale

Not applicable.

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since 1st dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, including respiratory rate[d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[h]	X	X	X	X	X	X	X	X	X	X	X	X
MMSE[i]				X	X	X	X	X	X	X		
FAQ[i]				X	X	X	X	X	X	X		
Disease staging						X			X	X		
12-lead ECG[f]		X		X		X			X	X	X	X
NPI[o]				X		X			X	X		
CDR[i]						X			X	X		
ADAS-cog14[j]						X			X	X		
Neurological examination[e]						X			X	X	X	X

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since 1st dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Weight						X			X	X		X
Blood sample for PD & biomarkers[j]						X			X	X		
MRI (safety, volumetric and functional sequences)						X			X	X		
Tau PET (optional substudy)									X	X		
Amyloid PET (optional substudy)									X	X		
CSF sampling for PD & biomarkers (optional substudy)[k]									X	X		
C-SSRS	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X		
Clinical assessment of suicidal thinking and behavior	X	X	X	X	X	X	X	X			X	X
Dispense study drug	X[m]	X	X	X	X	X	X	X				

ADAS-cog = Alzheimer's Disease Assessment Scale - cognitive subscale, AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PET = positron emission tomography, QTcF = QTc interval calculated using Fridericia's formula, UNS = Unscheduled Visit

a: A window of ±3 days will be permitted for Visits 16 and 17. A window of ±7 days will be permitted for Visits 18 and 19. A window of ±10 days will be permitted for Visit 20 to 24 inclusive. These windows should be calculated from Extension Phase Day 1. A window of ±3 days will be permitted for the Follow-up Visit calculated from the last Extension Phase dose.

b: Subjects who permanently discontinue taking study drug before end of treatment will undergo an ED Visit within 7 days of their last dose of study drug. In addition, a Follow-Up Visit will be scheduled 4 weeks after the last dose of study drug.

c: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator.

d: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

e: A full neurologic examination will be performed at Visit 24 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs.

f: Single 12-lead standard ECGs will be recorded. If the QTc interval calculated using Fridericia's formula (QTcF) machine read is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

g: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	Extension											
Period	Treatment[a]										1 Month Follow-Up	UNS[c]
Day in Extension Phase	15	29	57	120	245	365	484	610	729	ED[b]		
Visit	16	17	18	19	20	21	22	23	24			
Weeks elapsed since 1st dose in Extension Phase	2	4	8	17	35	52	69	87	104			
Nominal months elapsed since 1st dose in Extension Phase	0.5	1	2	4	8	12	16	20	24			
Procedures/Assessments												

h: More frequent testing may be required per local regulations. If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

i: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

j: PD and biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose.

k: For subjects who consent to participate in the CSF longitudinal substudy. Visit 24 (or ED) also includes blood PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by lumbar puncture (LP) between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and International Normalized Ratio (INR) (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures.

l: New AEs to be collected 4 weeks post last dose, and followed-up until resolution, or until 12 weeks post last dose, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected

m: Visit 15 bottles are re-dispensed at Visit 16 after accountability is performed.

n: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

o: NPI-12 will be used if available, and both NPI-10 and NPI-12 scores calculated

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2609-G000-301

Study Protocol Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigational Product Name: Elenbecestat (E2609)

IND Number: 109308

EudraCT Number: 2016-003928-23

SIGNATURES

Authors (revised per Amendment 06):

PPD Neurology Business Group, Eisai Ltd.	Date
PPD Neurology Business Group, Eisai Ltd.	Date
PPD Neurology Business Group, Eisai Inc.	Date
PPD Neurology Business Group, Eisai Inc.	Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat (E2609)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Added details for the open-label Extension Phase	As indicated in the original protocol the Extension Phase details are included	Synopsis • Study Period and Phase of Development • Study Design • Objectives • Study Treatments • Inclusion Criteria • Duration of Treatment • Concomitant Drug/ Therapy • Assessments • Bioanalytical Methods • Statistical Methods Section 5.3 Section 9.1 Figure 1 Section 9.1.3 Section 9.1.3.1 Section 9.1.4 Table 5 Appendix 5 in Section 12
Pooling of study 301 and 302 analysis, with decreased subjects and sites in each study	Sample size re-estimation indicated the requirement for 1900 subjects compared with the original 1330 subjects per study. Studies will be combined to achieve the required numbers.	Synopsis • Site(s) • Core Study Objectives • Study Design • Number of Subjects • Statistical Methods Section 6 Section 8.1 Section 8.2 Section 9.1 Section 9.2.1 Section 9.3 Section 9.7.1.1 Section 9.7.2

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Study 202 summary of safety and efficacy added and its Extension Phase exposure	Emerging clinical data indicating acceptable safety and signals of clinical efficacy	Section 7.1 Section 9.4.4
Key secondary objectives defined	Three key secondary objectives have been defined from the multiple secondary objectives, indicating those of most importance that will be tested in a hierarchical manner if the primary objective is significant.	Synopsis • Core Study Objectives • Statistical Methods Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added Alzheimer's Disease Composite Score (ADCOMS) as a secondary objective for the Core Study	This novel endpoint has been included, aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change	Synopsis • Core Study Objectives, • Assessments • Study Endpoints Section 8.2 Section 9.2.1 Section 9.2.3 Section 9.5.1.3.1 Section 9.7.1.1.2 Section 9.7.1.6.2
Added of CDR-SB and ADCOMS enriched by baseline amyloid PET SUVR as a secondary objective for the Core Study	Elenbecestat may be more effective when amyloid reaches a minimum level but before too much is on board	Synopsis • Core Study Objectives, • Study Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added a biomarker objective and endpoints for the Core Study	Clarification	Synopsis • Core Study Objectives, • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 8.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Revised country list	To reflect that South Africa is a participating country	Synopsis • Study Design Section 9.1
Added that if subjects have	To clarify that subjects would	Synopsis

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator	not need to withdraw from study	• Study Design Section 9.1.2.1 Section 9.5.1.5.7
Added that CSF will be used to assess PD, PK, and exploratory biomarkers.	Clarification	Synopsis • Study Design Section 9.1.2.1
Added that CSF and PET assessments should be conducted before any other visit assessments and while the study is still study drug	Clarification	Synopsis • Study Design Section 9.1.2 Section 9.1.2.1
Added that new AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation	Clarification	Synopsis • Study Design Section 9.3.3
Historical cerebrospinal fluid (CSF) samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity	Allows historical CSF sample to be analyzed to determine eligibility	Synopsis • Inclusion Criteria • Assessments Section 9.3.1
Added that levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid analysis, if available in region	For flexibility on Vitamin B12 deficiency analysis	Synopsis • Exclusion Criteria Section 9.3.2 Table 3 Section 9.5.2.2 Table 6

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Revised exclusion criterion (#14) regarding a prolonged QTc interval calculated using Fridericia's formula (QTcF) was changed to clarify that if the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed.	Machine read QTcF values might be lower than central reads. Subjects are SF if the average of 3 ECGs on central read > 450 ms. Instructing sites to perform triplicate ECGs when machine reads are > 440 ms will ensure all required evaluations are completed.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.6 Table 5
Revised exclusion criterion (#19) to clarify that subjects who participated in a clinical study that involved a new chemical entity or investigational drug for Alzheimer's Disease (AD) are to be excluded	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
Added events of possible abuse potential to the safety assessments for the Core Study and Extension Phase	Clarification	Synopsis • Assessments Section 9.7.1.8
Revised text to clarify that if a Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice during the Treatment Period, that is confirmed on repeat testing and within a 6-month period, then the subject should be discontinued permanently from the study drug in the Core Study.	To clarify that this applies to Treatment Period in the Core Study.	Synopsis • Assessments Section 9.3.3
Added timepoints when the NPI-10 item will be conducted in the Extension Phase	Wording added	Synopsis • Assessments
Clarified that *ApoE4* status may be included in the model if appropriate	Clarification	Synopsis • Efficacy Analyses Section 9.7.1.6.1 Section 9.7.1.6.2

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Revised Core Study analysis of biomarker endpoints to clarify that change from baseline in functional magnetic resonance imaging (fMRI) parameters as appropriate, will be determined	Clarification	Synopsis • Analyses for Biomarker Endpoints Section 9.7.1.7.3
Added that a futility analysis is planned when approximately 30% of subjects have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date	Clarification	Synopsis • Interim Analyses Section 9.7.3
Clarified that subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will need to provide separate Extension Phase-specific written informed consent	Clarification	Section 5
Added a valid period for assessment results of Tiers 1 to 5	Clarification	Section 9.1.1.1
Added information to permanent discontinuation	Clarification to cover subjects where the study drug had been temporary suspended for more than 3 weeks	Section 9.3.3
Added that termination of therapy for symptomatic treatment of AD during the study should be undertaken in compliance with local standard of care.	Clarification	Section 9.4.7
Added information on CSF sampling at Visit 13 (early discontinuation [ED])	Clarification to avoid samples being taken when subject has been off the study drug for more than 7 days.	Section 9.5.1.3.3
Revised to clarify that postdose pharmacokinetic (PK) samples will not be needed for subjects who are temporary suspended from study drug or permanently stopped the study drug at the ED Visit	To clarify requirements for collection of PK samples when subjects are not being dosed.	Section 9.5.1.4.1
Added neurogranin as an	Correction	Table 2

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Exploratory Biomarker Subset		
Added details as to when amyloid positron emission tomography (PET) and tau PET imaging will be conducted	Clarification	Section 9.5.1.4.2
Added how adverse events (AEs) will be handled for subjects who permanently discontinue study drug, but continue in the study.	Wording added	Section 9.3.3 Section 9.5.1.5.1
Added treatment changes in depigmentation/hypopigmentation/ vitiligo/loss of hair color to the list of AEs that will require the collection of information to provide detailed description of the event	AE of interest added	Section 9.5.1.5.1
Revised blood sampling for immunological assessments and added corresponding footnote	Based on Data Safety Monitoring Board recommendation	Table 5 Table 6
Revised the example of the locally approved amyloid-imaging agent to Neuraceq	To reflect main imaging agent in use during the study	Table 4 Table 5
Added a footnote to state that Visit 2 bottles of study drug will be redispensed at Visit 3	Clarification	Table 5
Added footnotes to state when initiation, termination or change in dose is permitted and that herbal medications and preparations should be discussed with the medical monitor	Clarification	Listing 4 in Section 12
Revised list of permitted medication and permitted medication if used for short-term basis	Clarification	Listing 5 in Section 12
Added footnote that herbal medications or preparations should be discussed with the medical monitor and benzodiazepines were deleted	Clarification	Listing 5 and Listing 6 in Section 12

Revisions to Version 6.0

New version/date: Version 7.0/21 Jan 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to remove "(E2609)"; grammatical, typographical, and formatting changes were also made	Correction	Throughout

Revisions to Version 5.0

New version/date: Version 6.0/19 Jul 2018 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) that have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 4 Table 5 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 Table 5
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 Table 4 and Table 5
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 Table 5
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis • Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Core Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 Table 5
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection is exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or ECG at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 5) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis • Bioanalytical Methods • Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 Table 4
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 Table 5

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 Table 2
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 Table 4
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 Table 6
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result	Added for clarification	Section 11.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
documentation from the urine dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted “pharmacogenomics (PGx)” data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4 (new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSF collection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4 and Table 5)
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the medical monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.5
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14)	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 3) Section 9.5.2.1(Table 4 and Table 5)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for pharmacokinetic analysis during the treatment and follow-up periods; added specimen collection for coagulation; added clarification that the volumes are estimates and may vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 6
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 3 Section9.5.2.1, Table 4

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 4), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification to the exclusion criteria for absolute	Clarification to explain the standardized method of ALC	Synopsis • Exclusion Criteria

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	calculation used across sites	• Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 5
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the Treatment Period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.2.1 Section 9.5.2.1 (Table 4 and Table 5)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 5)
Blood volumes for PK, pharmacodynamic (PD), and	Corrected to align with the Schedule of Procedures/	Section 9.5.2.2, Table 6

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
exploratory biomarkers were revised	Assessments	
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs with symptomatic effects.	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made mandatory at the second of the follow-up visits.	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 5
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 3 Table 4 Table 5

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	DSMB for periodic review during the study	Table 6
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as secondary	Section 9.2.1
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat (E2609)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02) V4.0 04 Apr 2017 (Amendment 03) V5.0 28 Jun 2017 (Amendment 04) V6.0 19 Jul 2018 (Amendment 05) V7.0 21 Jan 2019 (Amendment 06)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements forPharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Approximately 250 global sites (revised per Amendment 06)

Study Period and Phase of Development

This Phase 3 study will consist of:

- Core Study: The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up
- Open-label Extension Phase: Up to 24 months of additional treatment, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first, and 1-month follow up. (revised per Amendment 06)

Core Study Objectives

Primary Objective

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD) pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 06)

Key Secondary Objectives (revised per Amendment 06)

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-301

Other Secondary Objectives (revised per Amendment 06)

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD

- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET standardized uptake value ratio (SUVR) pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale - cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE) and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] amyloid beta [Aβ] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels

(eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 06)

- To explore potential plasma and CSF biomarkers of Alzheimer's disease (AD) (eg, neurofilament [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 [YKL-40], and neurogranin [Ng]) (revised per Amendment 06)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

Exploratory Objectives

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Extension Phase Objectives (revised per Amendment 06)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with EAD

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on CDR-SB, ADCOMS, MMSE, FAQ,ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia, for subjects who were not clinically staged as

having dementia at Core Study baseline, based on a clinical diagnosis

- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by PET (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using vMRI
- To evaluate the long term-effect of elenbecestat in preserving brain connectivity as measured by task-free fMRI
- To evaluate the long-term effect of elenbecestat on CSF tau, p-tau, and Aβ levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, Ng)

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other AD pharmacotherapies
- To explore the long-term effect of elenbecestat on the NPI-10 and if available NPI-12

Study Design

The study consists of a Core Study followed by an open-label Extension Phase. The Core study is a 24-month treatment with a 3-month follow up, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 06)

Study E2609-G000-301 and Study E2609-G000-302 will be combined with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 06)

In this Core Study, subjects will be randomized in a double-blind manner to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China

6. Other Asian countries
7. South America

(revised per Amendments 01, 02, and 06)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET, tau PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. (revised per Amendments 05 and 06)

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. . The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 03 and 06).

Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 05) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, ISLT, and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

For any given subject, every effort should be made to ensure that the diagnosing clinician

(responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01, 02, and 04) Vital signs and weight will be recorded, and a single 12-lead ECG will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities that may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task-free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both. (revised per Amendment 04) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies, respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. Inclusion and exclusion criteria will be reviewed again, together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 02 and 05)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

In some cases, unscheduled (UNS) visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and is not within 3 months of a previous CSF sample). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug (revised per Amendment 05 and 06)

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the

24-month Treatment Period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 04) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 06) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 06)

Extension Phase

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

During the Extension Phase, the assessment of safety will include the recording of all AEs. In addition, vital signs, weight, safety blood and urine laboratory tests, ECGs [no central reading of ECGs], suicidality, neurological examination, NPI, and signals of abuse potential will continue to be assessed.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study) and at Visit 24/ED, but will be abbreviated for all other timepoints.

Clinical assessments will be performed every 4 months (MMSE, FAQ) or 12 months (CDR, ADAS-cog14). Blood biomarkers and MRI will be assessed every 12 months. Optional amyloid and

tau PET and CSF biomarker assessments will be conducted at the end of 2-year open-label treatment (Extension Phase).

Subjects who complete treatment in the Extension Phase or who discontinue the study drug are required to complete the Follow-up Visit, 1 month after the last dose.

Subjects may discontinue from the open-label study drug for any reason, but will be required to complete the ED Visit (within 7 days of last dose) and the Follow-up Visit 1 month after the last dose of study drug. In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3, are met. (revised per Amendment 06)

Number of Subjects

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 06)

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or mild AD disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau:Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility, but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 04 and 06).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a

stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications that are administered as short courses (eg, up to 3 weeks unless discussed and agreed with medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

Extension Phase (revised per Amendment 06)

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations).
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

Core Study

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)

- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 04 and 06)
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥1.7; bilirubin

≥1.5×ULN; albumin <lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during Screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below LLN or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 06)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 04)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection. (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 06)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo. (revised per Amendment 06)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Extension Phase

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food. (revised per Amendment 06)

Duration of Treatment

Core Study: The maximum estimated duration for each subject is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow up).

Extension Phase: The estimated duration for a subject is 25 months (ie, 24 months of treatment and 1-month follow up). (revised per Amendment 06).

Concomitant Drug/Therapy (both Core Study and Extension Phase)

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 02)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 02 and 04)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 03 and 06) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant

medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 04 and 06)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments (both Core Study and Extension Phase)

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD. ADCOMS (Wang, et al., 2016) is a composite clinical score that represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, of the MMSE, the CDR, and the ADAS-cog14. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change. (revised per Amendment 06)

Pharmacokinetic Assessments (Core Study Only)

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (both Core Study and Extension Phase)

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, 03, and 04)

Blood will be collected to measure PD and biomarkers in both the Core Study and the Extension Phase. (revised per Amendments 02, 03, 04, and 06)

Amyloid PET imaging or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 04) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor), but will not suffice for baseline assessment

if the subject wishes to consent to the amyloid PET longitudinal substudy. Historical CSF samples may be analyzed to confirm amyloid pathology, if collected, processed, and stored under appropriate conditions and approved by the sponsor. (revised per Amendments 04 and 06)

Subjects who consent to participate in the amyloid and tau-PET longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED Visit in the Core Study and at 24 months or at the ED Visit in the Extension Phase. (revised per Amendments 04, 05, and 06)

Subjects who consent to the CSF substudy will have samples taken at 24 months or at the ED Visit in both the Core Study and Extension Phase for PD and biomarker assessments. (revised per Amendment 06)

Safety Assessments (both Core Study and Extension Phase)

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings (evaluated by a central reader in the Core Study); physical, dermatologic, and neurologic examinations; assessment of suicidality, events of possible signals of drug abuse potential, and MRIs during the Treatment Period. (revised per Amendments 01 and 06)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when ALC returns to greater than 800/mm3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6-month period during the Core Study treatment, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period, then the subject should be discontinued permanently from the study drug. (revised per Amendments 01, 02, 04, and 06)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly until Month 3 of treatment in the Core Study and until Month 2 in the Extension Phase. Thereafter, they will be monitored every 3 months in the Core Study and every 4 months in the Extension Phase until the end of the Treatment Period and at Follow-up Visits. (revised per Amendment 06)

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period or during the first 4 weeks of the Follow-up Period in the Core Study and during the Extension Phase will require a more detailed follow up. (revised per Amendments 04 and 06)

Other Assessments (Core Study Only)

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Other Assessments (Extension Phase Only)

The NPI-10 or if available NPI-12 will be conducted at Day 1, Month 4, Month 12, and then every 12 months. If the NPI-12 questionnaire is used, both NPI-10 and NPI-12 scores will be generated. (revised per Amendment 06)

Bioanalytical Methods (both Core Study and Extension Phase)

CSF AD assessment (eg, tau:Aβ(1-42) ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits (revised per Amendment 04) Exploratory biomarkers such as neurofilament NFL, Ng, YKL-40, and VILIP1 may also be measured using validated assays. (revised per Amendments 02 and 06)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 04)

Plasma concentrations of elenbecestat that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 06)

Core Study

Study Endpoints
Primary Endpoint

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 06)

Key Secondary Endpoints (revised per Amendment 06)

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

Other Secondary Endpoints (revised per Amendment 06)

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies (revised per Amendment 01)
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies (revised per Amendment 01)
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in plasma amyloid biomarker eg, Aβ(1-x) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng (revised per Amendment 06)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization

- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 02, and 06) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD

medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendments 01 and 06)

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 06)

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 06)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. *ApoE4* status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as

having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 04, 05, and 06)

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 06)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last

assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha=0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, along with change from baseline

in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendments 01 and 06)

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Extension Phase (revised per Amendment 06)

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42)) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

Extension Phase Analysis Sets

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, FAS, PPS, and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline

will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive an increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al., 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, the MMRM model will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET SUVR
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change in baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline in Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints. The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at the time of the futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 06)

Sample Size Rationale

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 06)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCOMS	Alzheimer's Disease Composite Score
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating –Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system

Abbreviation	Term
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	early Alzheimer's disease
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)

Abbreviation	Term
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau

Abbreviation	Term
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SUVR	standardized uptake value ratio
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 04) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 04)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative or study partner). (revised per Amendment 04) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 05)

Subjects who agree to take part in the Extension Phase, and the substudies during the Extension Phase, will be asked to provide separate Extension Phase-specific written informed consent. At the start of the Extension Phase, an assessment of capacity to consent should be undertaken, and continue periodically throughout the Extension Phase treatment, utilizing the method and frequency as for the Core Study above. (revised per Amendment 06)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 250 investigational sites globally. (revised per Amendment 06)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ-secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat Investigator's Brochure). Another study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat was administered orally by gavage once a day to male rats for 28 days before, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 04) Further details of the nonclinical data to date with elenbecestat can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing to assess the PK levels of elenbecestat and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open-label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat. It also investigated the effects of elenbecestat on the PK properties of digoxin. (revised per Amendment 04)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open-label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open-label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat. (revised per Amendment 02)

Study E2609-G000-202 (Study 202) has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat given daily, along with safety and exploratory efficacy. Elenbecestat was generally well tolerated; no unexpected safety concerns emerged. Although sample sizes were small, statistically significant decreases in PET standardized uptake value ratios (SUVR) were seen. Clinical assessments suggest elenbecestat may have attenuating effects on cognitive decline in MCI-to-moderate AD subjects (Lynch, et al., 2018). Forty-three out of the 70 randomized subjects completed the study and of these 41 elected to enroll in an open-label Extension Phase. The Extension Phase has been running for 2 years and currently has 36 subjects still receiving elenbecestat. (revised per Amendment 06)

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat. In elderly subjects treated with 50 mg of elenbecestat, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects who were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or ECG parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of

latent infections in subjects who received single doses of elenbecestat. A single dose of elenbecestat up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat when coadministered with elenbecestat but not when dosed at least 2 hours apart from elenbecestat. Elenbecestat (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat. Based on these results, it is not considered necessary to impose restrictions during elenbecestat treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications that are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when elenbecestat will not be present, as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study

confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T-wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat. The effects of elenbecestat on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50-mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat PK parameters (C_{max} and AUC). (revised per Amendment 04) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the Core Study is:

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 06)

8.2 Secondary Objectives

The key secondary objectives of the Core Study are as follows (revised per Amendment 06):

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-301

The other secondary objectives of the Core Study are as follows (revised per Amendment 06):

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of CDR scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline

based on a clinical diagnosis evaluated every 3 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale - cognitive subscale14 ($ADAS\text{-}cog_{14}$), Mini Mental State Examination (MMSE) and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF total tau [t-tau] amyloid beta [Aβ] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], and functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 01)
- To evaluate the population PK of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 06)
- To explore potential plasma and CSF biomarkers of AD (eg, neurofilament [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 [YKL-40], and neuroganin [Ng]) (revised per Amendment 06)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)

- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD, as deemed appropriate To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

8.3 Exploratory Objectives

The exploratory objectives of the Core Study are:

- To explore the relationship between elenbecestat exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

For objectives specific to the Extension Phase, refer to Appendix 5 in Section 12.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group Core Study with an open-label Extension Phase in EAD including MCI due to AD (Albert et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow-up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 06)

Study E2609-G000-301 and Study E2609-G000-302 will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study.

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01, 02, and 06)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. (revised per Amendments 05 and 06)

The maximum estimated duration for each subject in the Core Study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow-up).

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days, (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase. (revised per Amendment 06)

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified

to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. (revised per Amendment 06) The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

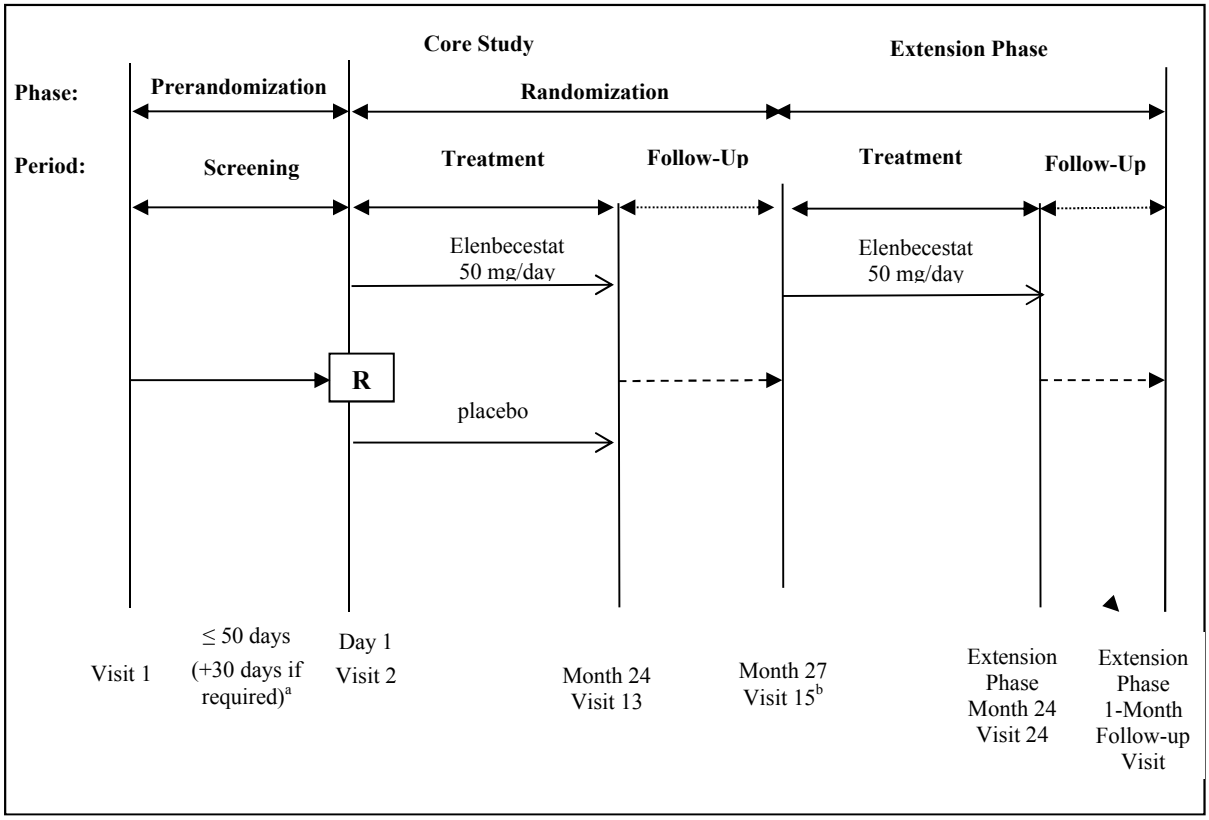

Figure 1 Study Design for E2609-G000-301 (revised per Amendment 06)

Elenbecestat = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a: Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

b: The last day of the Core Study (Visit 15) is also the first day of the Extension Phase

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained before the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5 (ie, during the Randomization Phase of the study). Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie, during the Randomization Phase of the study). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02, 04, and 05)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of Screening. (revised per Amendment 05)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Subjects may be re-screened, if deemed appropriate by the investigator and medical monitor. Unless otherwise stated, results of the following will be valid over the timeframes stated below (revised per Amendment 06):

- Tiers 1 to 3 Screening will be valid for 96 days from the date of assessment.
- Tier 4 MRIs will be valid for 90 days from the date of assessment.
- Tier 5 CSF results and amyloid PET scans will be valid for 90 days from the date of assessment, while historical amyloid PET scans will be valid for 12 months.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, ISLT, CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, before the CDR is administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 04)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart

rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs), which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 03 and 04) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities that may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment, or both. (revised per Amendment 04) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for lumbar puncture (LP) to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 04) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). The tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before

randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies, respectively. (revised per Amendment 04) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the LP. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of assessment for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 04) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05).

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 04 and 05).

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal

CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 02, 04, and 05) CSF and PET assessments should be conducted before any other visit assessments and while the subject is still on study drug. (revised per Amendment 06) Refer to Table 5 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04) Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED Visit/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD, and assessment of immune status are performed at different intervals throughout the Treatment Period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug. (revised per Amendments 02, 04, 05, and 06) Please refer to Schedule of Assessments (Table 5).

In some cases, unscheduled (UNS) visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-up Period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment on study drug and the 3-month follow up in the Core Study. The open-label Extension Phase will continue for 24 months, or until commercial availability of elenbecestat, or until a positive benefit-risk assessment in this indication is not demonstrated, whichever comes first (See Appendix 5 for full details of the Extension Phase). (revised per Amendments 03 and 06)

9.1.3.1 Extension Phase Follow-Up Period (revised per Amendment 06)

All subjects, regardless of whether they complete all 24 months of open-label treatment or discontinue study drug prematurely, will complete a post-treatment Follow-up Visit 1 month after the last dose of open-label study drug.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments in Appendix 5) will depend on the reason for the UNS visit and will be decided at the discretion of the investigator.

9.1.4 End of Study

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 03 and 06)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

Study E2609-G000-301 and Study E2609-G000-302 are multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group studies in subjects with EAD including MCI due to AD and the early stages of mild AD. The 2 studies will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study across 2 treatment groups, (placebo, 50 mg per day elenbecestat) for 24 months. (revised per Amendment 06) The maximum estimated duration for each subject on study is

anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month Follow-up Period).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment, and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog14 (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. A novel composite endpoint, ADCOMS (Wang, et al., 2016), is also included as a secondary endpoint. (revised per Amendments 01 and 06)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 04)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes

(eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). Therefore, attempts to slow disease progression with elenbecestat are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog14 immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical

meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

ADCOMS is a weighted linear combination of 12 items from 3 of the above clinical scales, the ADAS-cog, the MMSE, and the CDR. These 12 items consist of the predictive variables A4, A7, A8, A11, M1, M7, C1, C2, C3, C4, C5, and C6. The names of these items and the corresponding scale names are described in Table 1. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.

Table 1 Predictive Variables for the ADCOMS

Scale	Item ID	Item Name	PLS weight
ADAS-cog	A4	Delayed Word Recall	0.00847483
	A7	Orientation	0.017088
	A8	Word Recognition	0.003732761
	A11	Word Finding	0.016211
MMSE	M1	Orientation Time	0.041567
	M7	Drawing	0.038238
CDR	C1	Personal Care	0.054321
	C2	Community Affairs	0.1091
	C3	Home and Hobbies	0.089039
	C4	Judgment and Problem Solving	0.069493
	C5	Memory	0.058724
	C6	Orientation	0.078152

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale, CDR = Clinical Dementia Rating, ID = identification, MMSE = Mini Mental State Examination, PLS = Partial Least Squares.

(revised per Amendment 06)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat treatment.

9.2.4 Rationale for Biomarkers

CSF biomarkers, amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a LP procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 05)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ[1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendments 01 and 04)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 04) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 05)

Tau PET imaging will be performed to evaluate the effects of elenbecestat on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who

have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason, hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as NFL, Ng, VILIP1, or YKL-40) become available. (revised per Amendments 02, 03, and 06)

9.3 Selection of Study Population

At least 850 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 250 centers worldwide (revised per Amendment 06). Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau: Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 04 and 06).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per

Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

For inclusion criteria specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age

group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 04 and 06)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during Screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 06)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 04)

    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

NOTE: The following subjects do not need to be excluded:

- Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety. (revised per Amendment 04)
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTcF interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 06)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 06)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery that requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when ALC returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments (Table 5) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing occurs twice within a 6-month period during the Core Study, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period then the subject should be discontinued permanently from study drug. (revised per Amendments 01, 02, 04, and 06)

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 02 and 03) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 03)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 03)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 03)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study

drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

For subjects who temporarily suspend study drug (eg, ALC <800/mm^3) but progress to permanently discontinue study drug, the ED and Follow-up Visits should be scheduled as follows: (revised per Amendment 06)

- If ≥3 weeks from the last dose, then the ED Visit should be scheduled immediately, and the 1 month Follow-up Visit will not be required
- If <3 weeks from the last dose, then the ED Visit should be scheduled immediately, and Follow-up Visits at 1 and 3 months after the last dose will be required

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 06) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

Core Study

For this study, the test drug is elenbecestat and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 5 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the Treatment Period, the investigator should discuss with the medical monitor whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

For details on treatment to be administered in the Extension Phase, refer to Appendix 5 in Section 12.

9.4.2 Identity of Investigational Product(s)

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat

- Test drug code: E2609
- Generic name: elenbecestat
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) along with safety and exploratory efficacy of 5, 15, and 50 mg of elenbecestat given daily. Based on the PK/PD modeling results,

elenbecestat 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 03) Based on these data, elenbecestat 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 02)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 02 and 04)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 03 and 06) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 04 and 06)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable

- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 4 and Table 5. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a

clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment, and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog14: The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-cog14 that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-cog14. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0 to 10. (revised per Amendment 03)

ADCOMS: ADCOMS is a composite score of 12 items from the CDR, MMSE, and ADAS-cog, and does not require any additional assessments. (revised per Amendment 06)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 4 and Table 5, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7 to 10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available for screening to determine subject eligibility for the study. (revised per Amendment 03) Subjects who undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal.

CSF samples at Visit 13 should be collected while the subject is still on the study drug and before the other visit assessments. All ED CSF samples need to be taken no later than 7 days

after the last dose of study drug. All CSF samples should be taken at approximately the same time of day as at the Screening Visit. (revised per Amendment 06)

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to the CSF procedure at Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat. Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 04) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 4 and Table 5. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose PK samples are not required. (revised per Amendment 06)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 2 lists PD, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 04)

Table 2 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (revised per Amendment 06)

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Example of Exploratory Biomarkers	PD	Example of Exploratory Biomarkers
Whole Blood/ Plasma	*ApoE* [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) Aβ42/Aβ40 ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 Tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)
a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 03 and 04)

The plasma samples will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 03 and 04)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 4 and Table 5. (revised per Amendment 03) The blood sample collected for PD/exploratory biomarker analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 04)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the

event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 03 and 04) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 04) The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

For subjects participating in the amyloid PET substudy, amyloid PET imaging will be conducted on separate days from the scheduled visits and should be conducted before the clinic Visit 9 and no later than 7 days after the last dose for Visit 13/ED. (revised per Amendment 06)

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 05)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

For subjects participating in the tau PET substudy, tau PET imaging will be conducted on separate days from the scheduled visits and should be conducted before clinic Visit 13/ED and no later than 7 days after the last dose of study drug. (revised per Amendment 06)

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities that will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 05)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 4 and Table 5); and MRIs as detailed in Table 4 and Table 5. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 4 and Table 5. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs that will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendments 01 and 06)

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF until 4 weeks post last dose, and followed up for 12 weeks, or until resolution, whichever comes first (as shown in Table 5). Adverse events relating to study procedures will be collected until the end of study participation. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. (revised per Amendment 06)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog14, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines), (revised per Amendment 04)

Euphoria-related terms: (revised per Amendment 04)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 04)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 04)

- Somnolence (revised per Amendment 04)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 04)

- Psychosis
- Aggression (revised per Amendment 04)
- Confusion and disorientation (revised per Amendment 04)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 04)

- Drug tolerance
- Habituation (revised per Amendment 04)

- Substance related disorders (revised per Amendment 04)

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug): (revised per Amendment 04)

- Drug withdrawal syndrome (revised per Amendment 04)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the medical monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); treatment-emergent depigmentation/hypopigmentation/vitiligo/loss of hair color; amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendments 03 and 06)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. Table 4 and Table 5 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time), and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 02 and 03). A prothrombin time and INR should also be performed before LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 (with reflex MMA if available for low vitamin B12) (revised per Amendment 06) Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs, which will be stored for testing if required. (revised per Amendments 01 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, MMA = methylmalonic acid, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 4 and Table 5 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 5. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 4 and Table 5. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 03) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 5 and will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 4 and Table 5. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendments 01 and 06)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 4 and Table 5. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 06)

9.5.1.5.8 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 5).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 4 and Table 5, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 03) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 03) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the medical monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 5 presents the schedule of procedures/assessments for the Randomization Phase.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 04)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendment 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendment 04)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 03)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 05)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 04 and 05)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QTcF = QTc interval calculated using Fridericia's formula, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. (revised per Amendment 05)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, before the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report,

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1

(3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR, derived from the prothrombin time, and aPTT are to be performed as part of Screening. (revised per Amendments 02 and 03).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 04) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 03)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Neuraceq, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 90 days from the date of the original screening procedure. (revised per Amendments 05 and 06)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 2 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendments 05 and 06)

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Consent (subject and study partner)															X[dd]	
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X														X[dd]	
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (revised per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments (revised per Amendment 03)[ee]	X	X	X	X	X	X	X	X								
PBMCs for storage and testing required (revised per Amendment 06)	X					X		X				X	X			

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X[dd]	X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog14[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI-10	X					X		X		X		X	X		X[hh]	
C-SSRS	X	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X	X		X[dd]	
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X[ii]	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X		X[cc]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Tau PET (optional substudy)[u]												X	X		X[cc]	
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[y]												X	X		X[cc]	
Adverse events[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[b]	X	X	X	X	X	X	X	X	X	X				X[dd]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

Notes:

ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, QTcF = QTc interval calculated using Fridericia's formula, UNS = unscheduled, vMRI = volumetric MRI.

a: A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visits 7 to 13 inclusive (including for subjects who discontinue study drug early but who return for clinical assessments at 12 and 24 months). These windows should be calculated from Day 1. A window of ±3 days calculated from the last dose will be permitted for the Follow-up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS-cog14) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, only AEs relating to study procedures will be collected. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-up Visits (Visit 14 and Visit 15).

c: All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Visit 15 will also act as Baseline for subjects who successfully complete the Core Study and will be enrolled into the open-label Extension Phase. (revised per Amendments 01, 02, and 06)

d: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.e: Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15, or if the subject is continuing in the Extension Phase.

f: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

g: A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED) and Visit 15 if entering the Extension Phase (revised per Amendment 06) Neurologic examinations at the other visits will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h: Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i: Single 12-lead standard ECGs will be recorded. If the QTcF machine read is greater than 440 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values. (revised per Amendment 06)

j: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k: More frequent testing may be required per local regulations. (revised per Amendment 04) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m: Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 04)

n: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

o: Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

p: The clinical assessment of suicidality will require input from both the subject and the study partner

q: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

r: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

s: MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the medical monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t: Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuraceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 04 and 05)

u: For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 05)

v: Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w: Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, then postdose PK samples are not required.

x: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 01, 03, and 04)

y: For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 02, and 04)

z: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

aa: AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendments 05 and 06)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	**UNS Visit**[d]
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																

reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 02 and 04)

bb: The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Visit 2 bottles are re-dispensed at Visit 3 after accountability is performed. (revised per Amendment 06)

cc: Only for Extension Phase subjects who did not participate in optional longitudinal substudies in the Core Study but who wish to consent to optional longitudinal substudies in the Extension Phase

dd: For subjects entering the Extension Phase only

ee: Immunological assessments only required for subjects randomized before 07 Sep 2018

ff: New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, AEs relating to study procedures will be collected only

gg: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

hh: For those subjects entering the Extension Phase, NPI-12 will be used if available and both NPI-10 and NPI-12 scores calculated.

ii: Not required for those entering Extension Phase

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 4 and Table 5 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 4). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 6 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 03) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 03)

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 03 and 04)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 04)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 03 and 04)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 03)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 03 and 04)	1	None	1×3.5 mL	none	3.5 mL

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening and MMA where available (revised per Amendments 03, 04, and 06)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments Amendments 01, 04, and 06)[b]	8	none	1×10 mL	7×10 mL	80 mL
Blood for PBMCs (revised per Amendment 06)	4	none	1×10 mL	3×10 mL	40 mL
Blood for immune status (revised per Amendment 04)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 04)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 02, 03 and 04)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendments 02 and 03)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 02, 03, 04, and 06)		25.8 mL	46.8 mL	298.9mL	371.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit); actual volume may vary based on local regulations. (revised per Amendment 03)
b: Immunological assessment samples not required for subjects randomized after 07 Sep 2018 - reducing total blood volume to 291.5 mL (revised per Amendment 06)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 4 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. (revised per Amendment 06)

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 04)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 04)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (ocular herpes, new onset seizures, and symptomatic cerebral vasogenic edema), as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 5 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

For statistical methods specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 06)

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 06)

9.7.1.1.2 SECONDARY ENDPOINTS

The key secondary endpoints of the study are as follows (revised per Amendment 06):

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

The other secondary endpoints of the study are as follows (revised per Amendment 06):

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies (revised per Amendment 01)
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies (revised per Amendment 01)
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies (revised per Amendment 01)

9.7.1.1.3 BIOMARKER ENDPOINTS

The biomarker endpoints of the study are:

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

9.7.1.1.4 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog14, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization [Visit 2] [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendments 01, 02, and 06) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model. Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendments 01 and 06)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 06):

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 06)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. ApoE4 status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06) Proportion of subjects with

dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 01, 04, 05, and 06) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, with treatment group and randomization stratification variables, as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 06)

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$) derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)

- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 06)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 06)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 06)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendments 01 and 06)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 04)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will

be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog14, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 06)

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined two studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 06)

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during

DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter. (revised per Amendment 06)

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 02 and 04)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a] Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 04)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Initiation, termination or change in dose is permitted if in line with local standard of care. Any changes are required to be stable for 4 weeks before any cognitive assessments.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of cognitive enhancements then they should follow the same rules as the medications in this listing. (revised per Amendment 06)

Listing 5 Medications Permitted if Used on PRN or Short Term Basis (2 to 4 Weeks) Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Benzodiazepines (revised per Amendments 04 and 06)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Sedatives	
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	

PRN = Pro re nata

This list is not exhaustive.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of negative effects on cognition then they should follow the same rules as the medications in this listing. (revised per Amendment 06)

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 04)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 04)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts

Categories (revised per Amendment 04)			**Examples**[a]	
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 04)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 04)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	

Categories (revised per Amendment 04)			**Examples**[a]	
(revised per Amendment 04)	**17**	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 04)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 04)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 04)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 04)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 04) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

Appendix 5 Open-label Extension Phase (revised per Amendment 06)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on Clinical Dementia Rating –Sum Of Boxes (CDR-SB), Alzheimer's Disease Composite Score (ADCOMS), Mini Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14), and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia for subjects who were not clinically staged as having dementia at Core Study baseline, based on clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by positron emission tomography (PET) (optional substudies)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using volumetric magnetic resonance imaging (vMRI)
- To evaluate the long-term effect of elenbecestat in preserving brain connectivity as measured by task-free functional magnetic resonance imaging (fMRI)
- To evaluate the long-term effect of elenbecestat on cerebrospinal fluid (CSF) t-tau, phosphorylated-tau (p-tau), and amyloid beta (Aβ) levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL),visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin [Ng])

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other Alzheimer's disease (AD) pharmacotherapies
- To explore the long-term effect of elenbecestat on the Neuropsychiatric Inventory (NPI)-10 and if available NPI-12

Eligibility Criteria

Subjects who do not meet all of the inclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations).
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Study Design and Plan

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 24 months (2 years), or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first.

Subjects who are enrolled and complete the Core Study, including the 3-month Follow-up Period, will have the option to participate in the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not provide consent to transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

Subjects may discontinue from the open-label study drug for any reason but are required to complete the Early Discontinuation (ED) Visit (within 7 days of last dose). In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3 (Removal of Subjects from Therapy or Assessment) are met.

Subjects who complete the 24 months of Extension Phase treatment, or discontinue the study drug are required to complete the Follow-up Visit, 1 month after their last dose. The study will end when the last subject has completed the last Extension Phase study visit.

Treatment

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food.

Assessments

Assessments will be conducted as shown in Table 5 Visit 15 (Day 1 of the Extension Phase) and as shown in Table 9, for all other Extension Phase visits following the guidelines as indicated for the Core Study in Section 9.5. Concomitant therapy is allowed as stated in Section 9.4.7 and treatment compliance and accountability will be performed as indicated inSection 9.4.8, and Section 9.4.9, respectively.

Safety assessments (physical examinations, neurological examinations, vital signs, safety laboratory tests, ECGs [no central reading of ECGs], signals of potential abuse, pregnancy test for females of child-bearing potential, Columbia Suicide Severity Rating Scale (C-SSRS), and assessment of suicidal thinking/behavior, immunological assessments, safety magnetic resonance imaging (MRI) will be monitored according to Table 9 and all adverse events (AEs) and serious adverse events (SAEs) recorded.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study), and at Visit 24/ED, but will be abbreviated for all other timepoints.

Safety laboratory blood tests will be collected as indicated in Table 9 and analyzed by a central laboratory.

Blood samples for pharmacodynamic (PD) and biomarker analyses (Table 7) will be collected as indicated in Table 9. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Subjects that have consented to the optional CSF substudy (either at the start of the Core Study or Extension Phase) will have samples taken as indicated in the Table of Assessments to analyze PD and biomarkers (Table 7). Longitudinal CSF sample is taken before other Visit 24 assessments and whilst subject is still on study drug; for ED, CSF should be taken and no longer than 7 days after the last dose.

Safety brain MRI, vMRI, and fMRI assessments will be performed at the end of the Extension Phase Treatment Period (Visit 24 or ED). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be conducted centrally. If subjects have non-MRI compatible devices fitted during the Extension Phase treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator.

Table 7 Extension Phase Samples

Sample	PD	AD Biomarkers	Example of Exploratory Biomarkers
Blood	Aβ(1-x)		Tau NFL VILIP1 YKL-40
CSF		Aβ(1-42) Tau p-tau	NFL Neurogranin VILIP1 YKL-40

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), CSF = cerebrospinal fluid, NFL = neurofilament light, VILIP1 = visinin like protein 1, YKL 40 = human cartilage glycoprotein-39

Optional amyloid and tau PET assessments will be performed at the end of the Extension Phase Treatment Period before other Visit 24/ED assessments and when subjects are still on the study drug and no more than 7 days after the last dose of study drug. Subjects may consent to participate in the PET substudies at the start of the Extension Phase, for whom an additional assessment will be conducted at Visit 15 (before the first dose of the open-label study drug). PET scan acquisition and interpretation will be conducted centrally.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the start of the Extension Phase and at the end of treatment and a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive answer to any clinical assessment of suicidality question (subject or study partner) requires the C-SSRS to be performed; any positive finding on the C-SSRS requires a psychiatric evaluation to be conducted.

Clinical assessments (MMSE, FAQ, CDR, ADAS-cog14, disease staging, NPI) will be administered as described in the Schedule of Assessments (Table 9) and a central review employed to ensure global standardization. If available the NPI version 12 (NPI-12) questionnaire will be used, but both NPI-10 and NPI-12 scores will be calculated.

The Follow-up Visit will take place at 1 month after the last dose of study drug as described in Table 9. These assessments will also be performed if a subject prematurely discontinues from the Extension Phase.

The number of blood samples and the total volume of blood that will be collected throughout the Extension Phase, are summarized in Table 8.

Table 8 Summary of Sample Volumes

Assessment	Total Number Of Collection Time Points[a]	Number Of Time Points x Volume Per Collection (mL)	Total Volume (mL)
		Extension Phase Treatment and Follow-Up Periods	
Blood			
Safety labs	11	11×6.3 mL	69.3 mL
PD & biomarker sample	3	3×6 mL	18 mL
Total volume blood collected			**87.3 mL**
CSF PD and biomarker	2[a]	2×12 mL	24 mL

CSF = cerebrospinal fluid, PD = pharmacodynamic
a: For subjects who consented to the CSF substudy in the Core Study, only 1 sample (12 mL) is required to be collected

EXTENSION PHASE STATISTICAL METHODS

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall):
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline, based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

EXTENSION PHASE ANALYSIS SETS

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, Full Analysis Set (FAS), Per Protocol Analysis Set (PPS), and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al., 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, a mixed effects model for repeated measures (MMRM) will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET standardized uptake value ratio (SUVR)
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints.

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Sample Size Rationale

Not applicable.

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since 1st dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, including respiratory rate[d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[h]	X	X	X	X	X	X	X	X	X	X	X	X
MMSE[i]				X	X	X	X	X	X	X		
FAQ[i]				X	X	X	X	X	X	X		
Disease staging						X			X	X		
12-lead ECG[f]		X		X		X			X	X	X	X
NPI[o]				X		X			X	X		
CDR[i]						X			X	X		
ADAS-cog14[j]						X			X	X		
Neurological examination[e]						X			X	X	X	X

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since 1st dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Weight						X			X	X		X
Blood sample for PD & biomarkers[j]						X			X	X		
MRI (safety, volumetric and functional sequences)						X			X	X		
Tau PET (optional substudy)									X	X		
Amyloid PET (optional substudy)									X	X		
CSF sampling for PD & biomarkers (optional substudy)[k]									X	X		
C-SSRS	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X		
Clinical assessment of suicidal thinking and behavior	X	X	X	X	X	X	X	X			X	X
Dispense study drug	X[m]	X	X	X	X	X	X	X				

ADAS-cog = Alzheimer's Disease Assessment Scale - cognitive subscale, AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PET = positron emission tomography, QTcF = QTc interval calculated using Fridericia's formula, UNS = Unscheduled Visit

a: A window of ±3 days will be permitted for Visits 16 and 17. A window of ±7 days will be permitted for Visits 18 and 19. A window of ±10 days will be permitted for Visit 20 to 24 inclusive. These windows should be calculated from Extension Phase Day 1. A window of ±3 days will be permitted for the Follow-up Visit calculated from the last Extension Phase dose.

b: Subjects who permanently discontinue taking study drug before end of treatment will undergo an ED Visit within 7 days of their last dose of study drug. In addition, a Follow-Up Visit will be scheduled 4 weeks after the last dose of study drug.

c: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator.

d: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

e: A full neurologic examination will be performed at Visit 24 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs.

f: Single 12-lead standard ECGs will be recorded. If the QTc interval calculated using Fridericia's formula (QTcF) machine read is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

g: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	Extension											
Period	Treatment[a]										1 Month Follow-Up	UNS[c]
Day in Extension Phase	15	29	57	120	245	365	484	610	729	ED[b]		
Visit	16	17	18	19	20	21	22	23	24			
Weeks elapsed since 1st dose in Extension Phase	2	4	8	17	35	52	69	87	104			
Nominal months elapsed since 1st dose in Extension Phase	0.5	1	2	4	8	12	16	20	24			
Procedures/Assessments												

h: More frequent testing may be required per local regulations. If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

i: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

j: PD and biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose.

k: For subjects who consent to participate in the CSF longitudinal substudy. Visit 24 (or ED) also includes blood PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by lumbar puncture (LP) between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and International Normalized Ratio (INR) (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures.

l: New AEs to be collected 4 weeks post last dose, and followed-up until resolution, or until 12 weeks post last dose, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected

m: Visit 15 bottles are re-dispensed at Visit 16 after accountability is performed.

n: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

o: NPI-12 will be used if available, and both NPI-10 and NPI-12 scores calculated

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2609-G000-301

Study Protocol Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigational Product Name: Elenbecestat (E2609)

IND Number: 109308

EudraCT Number: 2016-003928-23

SIGNATURES

Authors (revised per Amendment 06):

PPD

Neurology Business Group, Eisai Ltd. — Date

PPD

Neurology Business Group, Eisai Ltd. — Date

PPD

Neurology Business Group, Eisai Inc. — Date

PPD

Neurology Business Group, Eisai Inc. — Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat (E2609)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 5.0

New version/date: Version 6.0/19 Jul 2018 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) who have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 3 Table 4 Section 9.7.1.1.4 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 4)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 3 and Table 4)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1(Table 4)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis • Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD)	Revised for clarification, since since CSF assessment of brain amyloid pathology will also include other biomarkers	Synopsis • Conduct of the Study • Inclusion Criteria • Pharmacodynamic,

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
biomarkers for brain amyloid pathology.		Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Core Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 4) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis • Bioanalytical Methods • Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.4 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 3)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 4)

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 1)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 3)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 5)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result	Added for clarification	Section 11.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
documentation from the urine dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted “pharmacogenomics (PGx)” data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4 (new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 3 and Table 4)
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 22 Section 9.5.2.1 (Table 3 and Table 4)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.5
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog_{14})	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 22) Section 9.5.2.1(Table 3 and Table 4)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for pharmacokinetic analysis during the treatment and follow-up periods; added specimen collection for coagulation; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 5
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 22 Section9.5.2.1, Table 3

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 3), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 22) Section 9.5.2.1 (Table 3 and Table 4)
Added clarification to the exclusion criteria for absolute	Clarification to explain the standardized method of ALC	Synopsis • Exclusion Criteria

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	calculation used across sites	• Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 22 Section 9.5.2.1, Table 4
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.2.1 Section 9.5.2.1 (Table 3 and Table 4)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 4)
Blood volumes for PK, pharmacodynamic (PD), and	Corrected to align with the Schedule of Procedures/	Section 9.5.2.2, Table 5

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
exploratory biomarkers were revised	Assessments	
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	with symptomatic effects.	Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 4

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
mandatory at the second of the follow-up visits.		
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the DSMB for periodic review during the study	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 22 Table 3 Table 4 Table 5
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as	Section 9.2.1

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	secondary	
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 02)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02) V4.0 04 Apr 2017 (Amendment 03) V5.0 28 Jun 2017 (Amendment 04) V6.0 19 Jul 2018 (Amendment 05)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)

- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid positron emission tomography (PET), volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)

- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (International Shopping List Task [ISLT]). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 04) Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a

sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. (revised per Amendment 05)

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 05) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01, 02 and 04) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both. (revised per Amendment 04) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs

measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 02 and 05)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendment 05)

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24 month treatment period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 04) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive

amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility, but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04) The historical imaging data must be made available to the sponsor.

5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive

product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)

- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund et al, 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 04)
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
        1) evidence of treatment with direct antiviral combination therapy
        2) evidence of sustained virological response at least 12 weeks post-treatment

        The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 04)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection. (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further

investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)

- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 02 and 04)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 04)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with

study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, 03, and 04)

Blood will be collected to measure PD and exploratory biomarkers at Visit 2 and various time points during treatment and follow-up. (revised per Amendments 02, 03, and 04)

Amyloid PET imaging or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 04) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor), but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04)

Subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will receive assessments accordingly at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendments 04 and 05) PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 03)

Exploratory biomarkers in CSF and/or plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 04)

T-tau and p-tau (neurodegenerative [NDG] biomarkers) in CSF, which are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), as well as plasma tau will be measured. NDG biomarkers have been demonstrated to increase in parallel with disease progression. (revised per Amendment 04)

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic

examinations; assessment of suicidality; and MRIs during the Treatment Period. (revised per Amendment 01)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. (revised per Amendment 04) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period or during the first 4 weeks of the Follow-up Period will require a more detailed follow-up. (revised per Amendment 04)

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF AD assessment (eg, Aβ [1-42], tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits (revised per

Amendment 04) Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 02)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 04)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis (revised per Amendment 01)
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog_{14} Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609)

treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ)

and changes in each of the biomarkers (amyloid PET, tau PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. (revised per Amendment 05) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at

a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating –Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio

Abbreviation	Term
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily

Abbreviation	Term
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 04) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 04)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative or study partner). (revised per Amendment 04) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 05)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat (E2609) was administered orally by gavage once a day to male rats for 28 days prior to, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 04) Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. (revised per Amendment 04)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 02)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat, (E2609) tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline

of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). (revised per Amendment 04) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)

- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. (revised per Amendment 05)

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days, (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

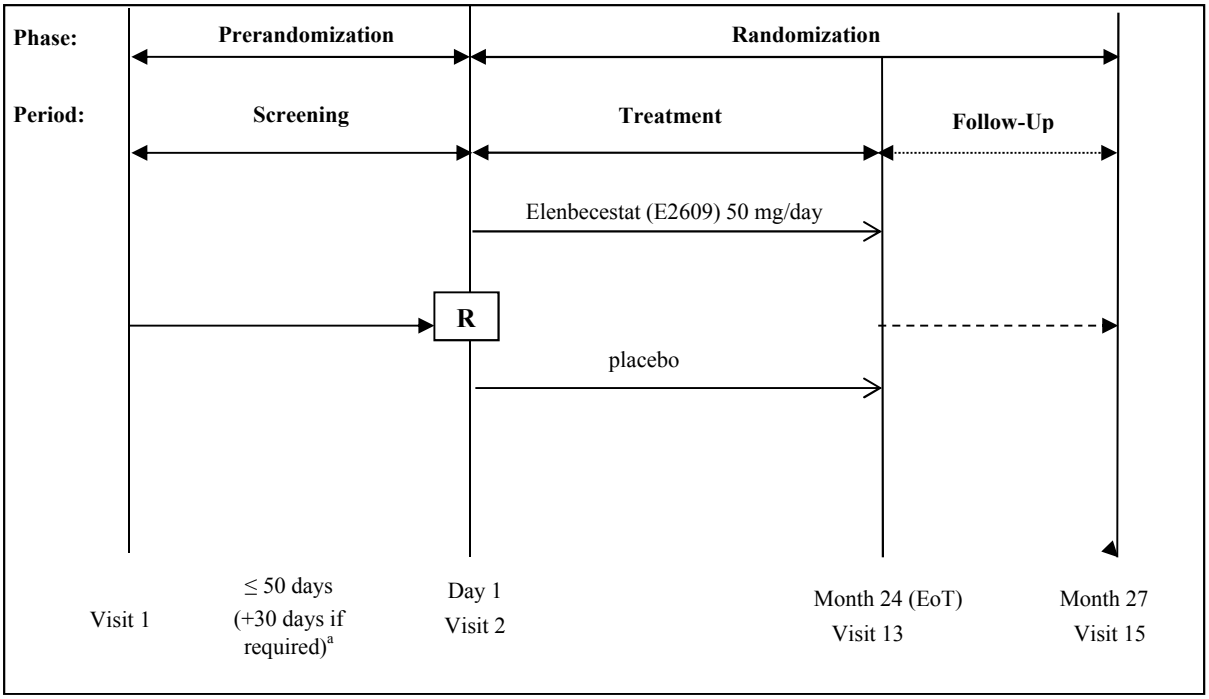

Figure 1 Study Design for E2609-G000-301

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 05)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the

Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02, 04, and 05)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of screening. (revised per Amendment 05)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to

progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 04)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs), which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 03 and 04) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need

to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment, or both. (revised per Amendment 04) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for LP to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 04) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Screening amyloid PET and/or Screening CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies, respectively. (revised per Amendment 04) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the lumbar puncture. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of scanning for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 04) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 05)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 04 and 05)

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will receive assessments accordingly at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 02, 04, and 05) (Refer to Table 4 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04) Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as required.

(revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core

Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 02, 04, and 05) Please refer to Schedule of Assessments (Table 4).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject

on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. (revised per Amendment 01)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 04)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to

ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog_{14} immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical

meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in a subset of subjects with EAD (revised per Amendment 05)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 05)
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 05)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 05)

CSF biomarkers, amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 05)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendments 01 and 04)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 04) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 05)

Tau PET imaging will be performed to evaluate the effects of elenbecestat (E2609) on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 03)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild

dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, Aβ(1-42), tau: Aβ(1-42) ratio) (revised per Amendment 04)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04) The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute

illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must

agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 04)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy

      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 04)

    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 04)

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination or vital signs at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety. (revised per Amendment 04)

    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant

neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - elenbecestat (E2609)

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. (revised per Amendment 04) If confirmed, study drug administration

should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 4) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 02 and 03) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 03)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 03)In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 03)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts

more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 4 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug

may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only

- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately70%. (revised per Amendment 03) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 02 and 04)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 04)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 3 and Table 4. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the

state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog$_{14}$. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 03)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 3 and Table 4, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available for screening to determine subject eligibility for the study. (revised per Amendment 03) Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 04) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 3 and Table 4. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit and within a maximum of 1 week after the last dose of study drug. A trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendments 03 and 04)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 1 lists pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 04)

Table 1 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Exploratory Biomarker Subset	PD	Exploratory Biomarkers Subset
Whole Blood/ Plasma	*ApoE* [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)
a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 03 and 04)

The plasma samples will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 03 and 04)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 3 and Table 4. (revised per Amendment 03) The blood sample collected for PD/exploratory biomarker analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 04)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation

(eg, treatment-emergent infection). (revised per Amendments 03 and 04) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 04) The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 04) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 05)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites)

in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities which will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 05)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 3 and Table 4); and MRIs as detailed in Table 3 and Table 4. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 3 and Table 4. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01)

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 4). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional

follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines), (revised per Amendment 04)

Euphoria-related terms: (revised per Amendment 04)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 04)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 04)

- Somnolence (revised per Amendment 04)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 04)

- Psychosis
- Aggression (revised per Amendment 04)
- Confusion and disorientation (revised per Amendment 04)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 04)

- Drug tolerance
- Habituation (revised per Amendment 04)

- Substance related disorders (revised per Amendment 04)

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug): (revised per Amendment 04)

- Drug withdrawal syndrome (revised per Amendment 04)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 03)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 2) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. Table 3 and Table 4 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time), and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 02 and 03). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs, which will be stored for testing if required. (revised per Amendments 01 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 3 and Table 4 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 4. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 3 and Table 4. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 03) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 4 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 3 and Table 4. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 3 and Table 4. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 4).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 3 and Table 4, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 03) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 03) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 4 presents the schedule of procedures/assessments for the Randomization Phase.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 04)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1
Blood samples for AD diagnostics and exploratory biomarkers[k] (revised per Amendment 04)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 03)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 05)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 04 and 05)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. (revised per Amendment 05)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase (revised per Amendment 05)

Phase	Prerandomization
Period	Screening
Visit	1

partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR, derived from the prothrombin time, and aPTT are to be performed as part of Screening. (revised per Amendments 02 and 03).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 04) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 03)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure. (revised per Amendment 05)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendment 05)

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 05)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (revised per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Tau PET (optional substudy) [u]												X	X			
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[y]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes:
ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

and Visit 15).

c All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) (revised per Amendments 01 and 02)

d Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

f Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

g A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). (revised per Amendment 01) Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

j If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k More frequent testing may be required per local regulations. (revised per Amendment 04) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 04)

n The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

o Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
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Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

p The clinical assessment of suicidality will require input from both the subject and the study partner

q There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

r There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

s MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuroceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 04 and 05)

u For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 05)

v Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

x PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 01, 03, and 04)

y For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301 (Revised per Amendment 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 02, and 04)

z Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

aa AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 02 and 04)

bb The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04)

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 3 and Table 4 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 3). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 5 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 03) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 03)

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 03 and 04)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 04)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 03 and 04)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 03)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 03 and 04)	1	None	1×3.5 mL	none	3.5 mL

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening (revised per Amendments 03 and 04)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendments 01 and 04)	14		1×20 mL	13×20 mL	280 mL
Blood for immune status (revised per Amendment 04)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 04)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 02, 03 and 04)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendments 02 and 03)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 02, 03 and 04)		25.8 mL	46.8 mL	458.9 mL	531.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit); actual volume may vary based on local regulations. (revised per Amendment 03)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 04)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 04)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 4 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 24 months using vMRI (revised per Amendment 01)
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a

sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes),

and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 01, 04, and 05) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 05)

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 05)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)

- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 01)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 04)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, , prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will

also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat

(E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 02 and 04)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a] Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 04)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Generic Name	**Trade Name**
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others (revised per Amendment 04)

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 04)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 04)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush

Categories (revised per Amendment 04)			**Examples**[a]	
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 04)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 04)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere (revised per Amendment 04)	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	

Categories (revised per Amendment 04)			**Examples**[a]	
Physical Dependence or Withdraw[b] (revised per Amendment 04)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 04)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 04)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 04)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 04) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

SIGNATURES

Authors:

PPD

Neuroscience Business Group, Eisai Ltd.

Date

PPD

Neuroscience Business Group, Eisai Ltd.

Date

PPD

Neuroscience Business Group, Eisai Ltd.

Date

PPD

Neuroscience Business Group, Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 4)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 3 and Table 4)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1(Table 4)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis • Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Core Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion Criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 4) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis • Bioanalytical Methods • Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.4 Section 9.7.1.7.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 3)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 4)

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 1)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 3)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 5)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result	Added for clarification	Section 11.3

Revisions to Version 4.0

New version/date: Version 5.0/28 Jun 2017 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
documentation from the urine dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted “pharmacogenomics (PGx)” data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4 (new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 3 and Table 4)
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 22 Section 9.5.2.1 (Table 3 and Table 4)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.5
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog_{14})	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 22) Section 9.5.2.1(Table 3 and Table 4)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for pharmacokinetic analysis during the treatment and follow-up periods; added specimen collection for coagulation; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 5
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 22 Section9.5.2.1, Table 3

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 3), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 22) Section 9.5.2.1 (Table 3 and Table 4)

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 22 Section 9.5.2.1, Table 4
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron	Time frame of 48 hours between PET tracer and CSF collections	Section 9.1.1.1

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 3 and Table 4)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 4)

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2, Table 5
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	with symptomatic effects.	Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 4

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
mandatory at the second of the follow-up visits.		
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the DSMB for periodic review during the study	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 22 Table 3 Table 4 Table 5
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as	Section 9.2.1

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	secondary	
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 02)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02) V4.0 04 Apr 2017 (Amendment 03) V5.0 28 Jun 2017 (Amendment 04)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid positron emission tomography (PET), volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (International Shopping List Task [ISLT]). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 04) Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04) All subjects will be

assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01, 02 and 04) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both. (revised per Amendment 04) For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to

participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 02)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24 month treatment period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 04) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of

eligibility.

b. CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) (revised per Amendment 04)

NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility, but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04) The historical imaging data must be made available to the sponsor.

5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:

- total abstinence (if it is their preferred and usual lifestyle)
- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund et al, 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 04)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 04)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection. (revised per Amendment 04)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 02 and 04)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 04)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination

are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog_{14} are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, 03, and 04)

Blood will be collected to measure PD and exploratory biomarkers at Visit 2 and various time points during treatment and follow-up. (revised per Amendments 02, 03, and 04)

Amyloid PET imaging or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 04) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor), but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04)

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug and that at least 6 months has elapsed since the prior PET scan was performed for subjects in the longitudinal PET substudy). (revised per Amendment 04) PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 03)

Exploratory biomarkers in CSF and/or plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 04)

T-tau and p-tau (neurodegenerative [NDG] biomarkers) in CSF, which are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), as well as plasma tau will be measured. NDG biomarkers have been demonstrated to increase in parallel with disease progression. (revised per Amendment 04)

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period. (revised per Amendment 01)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. (revised per Amendment 04) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period or during the first 4 weeks of the Follow-up Period will require a more detailed follow-up. (revised per Amendment 04)

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF AD assessment (eg, Aβ [1-42], tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits (revised per Amendment 04) Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 02)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 04)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis (revised per Amendment 01)
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per

Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing

values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy

endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating –Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate

Abbreviation	Term
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio

Abbreviation	Term
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily

Abbreviation	Term
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 04) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 04)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative or study partner). (revised per Amendment 04) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat (E2609) was administered orally by gavage once a day to male rats for 28 days prior to, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 04) Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. (revised per Amendment 04)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 02)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat, (E2609) tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline

of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). (revised per Amendment 04) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days, (plus an additional window of up to 30 days if required). (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in

the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

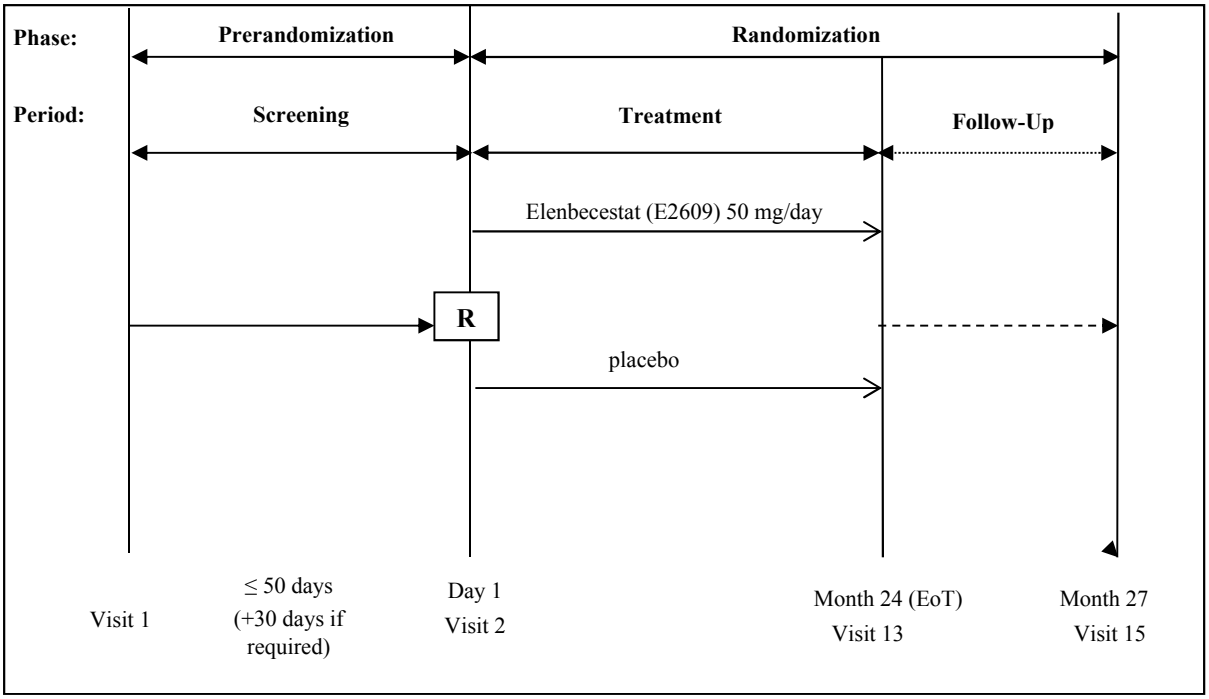

Figure 1 Study Design for E2609-G000-301

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 04)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study.

Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 04)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs), which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 03 and 04) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment, or both. (revised per Amendment 04) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those

subjects who, in the opinion of the investigator, are not suitable for LP to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 04) For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Screening amyloid PET and/or Screening CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies, respectively. (revised per Amendment 04) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the lumbar puncture. Results of Screening PET scans conducted specifically for this study will also be valid for 90 days from the date of scanning for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 04)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04)

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol (PET scans performed at ED should have a 6 months gap from the previous PET scan). Note that subjects who are assessed by both amyloid PET and CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) (Refer to Table 4 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04) Inclusion and exclusion

criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 04) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of

child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 04) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 02 and 04) Please refer to Schedule of Assessments (Table 4).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. (revised per Amendment 01)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether

inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 04)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects

(Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the

subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendments 01 and 04)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 04) This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and

it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 03)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 04)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be

restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.

b. CSF AD assessment (eg, Aβ(1-42), tau: Aβ(1-42) ratio) (revised per Amendment 04)

NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 04) The historical imaging data must be made available to the sponsor.

5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 04) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 04)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

- Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 04)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

- Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

  1) evidence of treatment with direct antiviral combination therapy

  2) evidence of sustained virological response at least 12 weeks post-treatment

  The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 04)

- A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 04)

- Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 04)

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination or vital signs at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety. (revised per Amendment 04)

- Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 04)

- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)

- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 04) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - elenbecestat (E2609)

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. (revised per Amendment 04) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 4) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 02 and 03) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 03)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 03)In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator

after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 03)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject’s discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 4 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry

N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At

enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately70%. (revised per Amendment 03) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the

code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 02 and 04)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 04)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator

- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the

designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 3 and Table 4. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic

examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD;

Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog_{14}. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 03)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 3 and Table 4, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available for screening to determine subject eligibility for the study. (revised per Amendment 03) Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 04) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 3 and Table 4. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit and within a maximum of 1 week after the last dose of

study drug. A trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendments 03 and 04)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 1 lists pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 04)

Table 1 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Exploratory Biomarker Subset	PD	Exploratory Biomarkers Subset
Whole Blood/ Plasma	*ApoE* [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)
a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 03 and 04)

The plasma samples will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening

and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 03 and 04)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 3 and Table 4. (revised per Amendment 03) The blood sample collected for PD/exploratory biomarker analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 04)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 03 and 04) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 04) The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at

least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 04) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 3 and Table 4); and MRIs as detailed in Table 3 and Table 4. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 3 and Table 4. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01)

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)

- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 4). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs that fall into the categories listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines), (revised per Amendment 04)

Euphoria-related terms: (revised per Amendment 04)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 04)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 04)

- Somnolence (revised per Amendment 04)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 04)

- Psychosis
- Aggression (revised per Amendment 04)
- Confusion and disorientation (revised per Amendment 04)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 04)

- Drug tolerance
- Habituation (revised per Amendment 04)
- Substance related disorders (revised per Amendment 04)

Physical dependence or withdraw (only for events observed within the first 4 weeks after the last dose of study drug): (revised per Amendment 04)

- Drug withdrawal syndrome (revised per Amendment 04)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 03)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 2) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize

the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. Table 3 and Table 4 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time), and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 02 and 03). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs, which will be stored for testing if required. (revised per Amendments 01 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 3 and Table 4 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 4. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 3 and Table 4. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 03) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 4 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 3 and Table 4. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 3 and Table 4. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 4).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 3 and Table 4, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 03) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 03) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 4 presents the schedule of procedures/assessments for the Randomization Phase.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 04)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Blood samples for AD diagnostics and exploratory biomarkers[k] (revised per Amendment 04)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 03)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 04)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR, derived from the prothrombin time, and aPTT are to be performed as part of Screening. (revised per Amendments 02 and 03).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 04) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 03)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 04)

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure.

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (revised per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[w]	X	X	X		X	X		X		X		X	X	X	X	

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CSF sampling for PK and PD (optional substudy)[x]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes:

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) (revised per Amendments 01 and 02)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). (revised per Amendment 01) Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] More frequent testing may be required per local regulations. (revised per Amendment 04) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 04)

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 04)

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 04) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuroceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior PET scan was performed. (revised per Amendment 04)

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 01, 03, and 04)

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 02, and 04)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 02 and 04)

[aa] The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 04)

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 3 and Table 4 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 3). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 5 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 03) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 03)

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 03 and 04)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 04)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 03 and 04)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 03)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 03 and 04)	1	None	1×3.5 mL	none	3.5 mL

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 04)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening (revised per Amendments 03 and 04)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendments 01 and 04)	14		1×20 mL	13×20 mL	280 mL
Blood for immune status (revised per Amendment 04)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 04)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 02, 03 and 04)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendments 02 and 03)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 02, 03 and 04)		25.8 mL	46.8 mL	458.9 mL	531.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit); actual volume may vary based on local regulations. (revised per Amendment 03)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 04)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 04)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 4 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 24 months using vMRI (revised per Amendment 01)
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability

criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes),

and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF Aβ(1-42), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 01 and 04) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 04)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI

- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 01)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or

- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 04)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, , prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will

also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat

(E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 02 and 04)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a] Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 04)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Generic Name	**Trade Name**
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others (revised per Amendment 04)

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 04)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 04)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush

Categories (revised per Amendment 04)			**Examples**[a]	
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 04)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 04)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere (revised per Amendment 04)	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	

Categories (revised per Amendment 04)			**Examples**[a]	
Physical Dependence or Withdraw[b] (revised per Amendment 04)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 04)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 04)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 04)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 04) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

SIGNATURES

Authors:

PPD

Eisai Ltd.

Date

PPD

Eisai, Inc.

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4 (new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 2 and Table 3)
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory	Corrected missing information	Section 9.2.4

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
biomarkers		
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 1 Section 9.5.2.1 (Table 2 and Table 3)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.5
Revidsed dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale ($ADAS\text{-}cog_{14}$)	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 1) Section 9.5.2.1(Table 2 and Table 3)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 3.0

New version/date: Version 4.0/04 April 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for pharmacokinetic analysis during the treatment and follow-up periods; added specimen collection for coagulation; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 4
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 1 Section9.5.2.1, Table 2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 2), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 3
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron	Time frame of 48 hours between PET tracer and CSF collections	Section 9.1.1.1

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 2 and Table 3)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 3)

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2, Table 4
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	with symptomatic effects.	Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 3

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
mandatory at the second of the follow-up visits.		
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the DSMB for periodic review during the study	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 1 Table 2 Table 3 Table 4
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as	Section 9.2.1

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	secondary	
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 02)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02) V4.0 04 Apr 2017 (Amendment 03)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that

determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory, PD (Aβ(1-x) and other isoforms), biomarker testing, and pharmacogenomics (PGx) analyses of *ApoE* genotype. (revised per Amendments 01 and 02) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken

and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 02)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as

appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant

medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before

dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
    - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
    - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
    - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendments 01 and 02)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB),

ophthalmic shingles or ocular herpes simplex virus (HSV) infection

- Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:

- any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
- elenbecestat (E2609)
- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 02)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake

cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood will be collected to measure plasma PD (Aβ1-x) at Screening and various timepoints during treatment and followup. (revised per Amendments 02 and 03)

Blood samples will be obtained at Screening and will be used for exploratory biomarker assessment and to determine the *ApoE* genotype of all subjects enrolled in this study. (revised per Amendments 01, 02, and 03)

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug). PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 03)

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendment 02)

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period. (revised per Amendment 01)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods. Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 02)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis (revised per Amendment 01)
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at

24 months (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to

treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to

dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or

memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs,

out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio

Abbreviation	Term
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula

Abbreviation	Term
R	randomization
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 02)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat, (E2609) tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the

lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5

metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

Preliminary PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All

subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

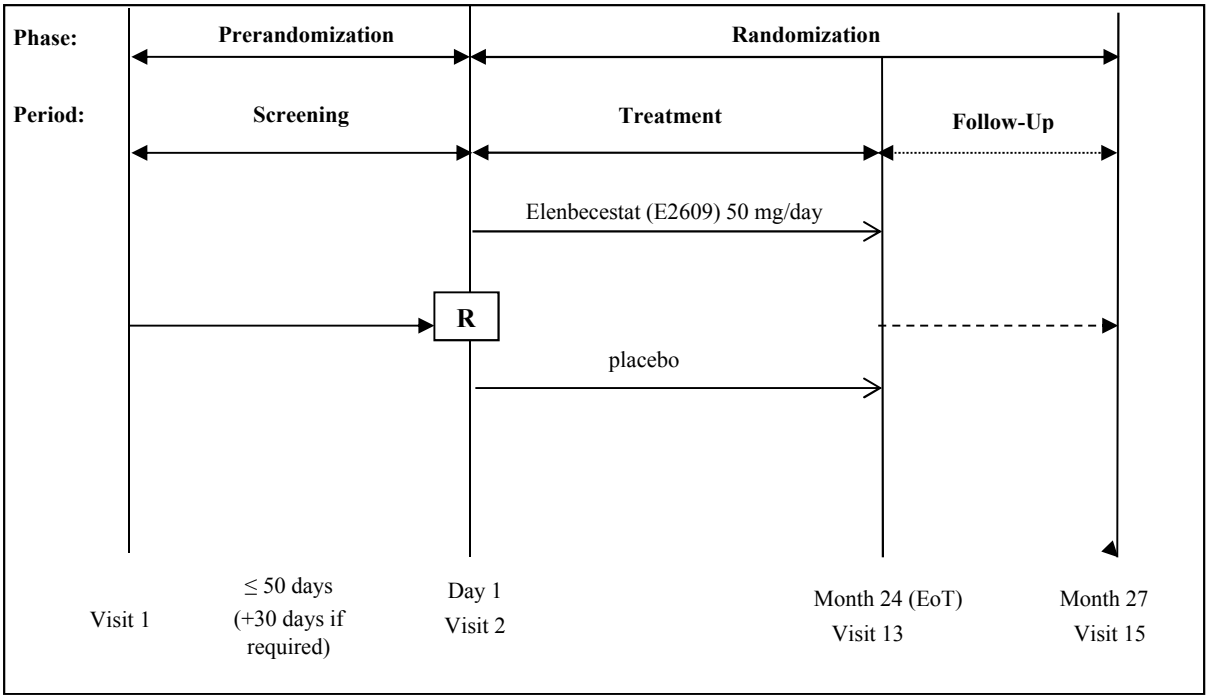

Figure 1 Study Design for E2609-G000-301

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF

substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarkers, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 03)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the

CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. (revised per Amendment 01)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by elenbecestat (E2609) increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD

progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog_{14} immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable

(Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability

of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 01)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 03)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

- Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

- any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat (E2609)

- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 02 and 03) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥

1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 03)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 03)In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 03)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to

return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by

manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately70%. (revised per Amendment 03) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 02)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 03) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:

(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus

(chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog$_{14}$. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 03)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake.

Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available for screening to determine subject eligibility for the study. (revised per Amendment 03) Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed.

Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendment 03)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. (revised per Amendment 03)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 activity levels will be measured using internally developed fluorescence resonance energy transfer and BACE protein levels will be measured using ELISA based assay(s). (revised per Amendment 03) Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 2 and Table 3. (revised per Amendment 03) The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day.

Blood samples for immunologic assessments and CSF (if applicable) collected at Screening will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendment 03) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror

will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 2 and Table 3. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01)

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated

suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 03)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 2) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time), and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 02 and 03). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing as required. (revised per Amendments 01 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 03) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 03)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 03) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 03) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and other biomarkers[j]	X (Tier 3)
Blood sample for immunologic assessments,	X (Tier 3)

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

including isolation of PBMCs for storage and testing as required (revised per Amendment 03)	
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 03)	X (Tier 5)

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time,INR, derived from the prothrombin time, and aPTT are to be performed as part of Screening. (revised per Amendments 02 and 03).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 03)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).
l: Only required for female subjects of child-bearing potential
m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.
n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure.
o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.
p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (reviser per Amendment 03)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and other biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional												X	X			

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
substudy)[x]																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes:

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) (revised per Amendments 01 and 02)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). (revised per Amendment 01) Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if

no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 01 and 03)

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 02)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that might indicate signals of possible drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire); categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3. (revised per Amendments 02)

[aa] The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 03) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 03)

Table 4 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)		Total Volume[a] (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry (revised per Amendment 03)	15	1×2.5 mL	14×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Coagulation (revised per Amendment 03)	15	1×1.8 mL	14×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 03)	1	1×2.5 mL	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendment 03)	1	None	1×3.5 mL	3.5mL
Vitamin B12 at Screening (revised per Amendment 03)	1	can use blood drawn for TFT	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendment 01)	15	1×20 mL	14×20 mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample (revised per Amendments 02 and 03)	10	1×24 mL	9×6 mL	78 mL
PK analysis (revised per Amendments 02 and 03)	7	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendment 03)	1	1×6 mL	none	6 mL
All blood samples, total volume collected (revised per Amendments 02 and 03)		61.3 mL	458.7 mL	520 mL
CSF				
Amyloid eligibility	1	1×12 mL	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit); actual volume may vary based on local regulations. (revised per Amendment 03)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their

last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is

planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI (revised per Amendment 01)
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendment 01) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate,

randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 01)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, , prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to

be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic or Ocular Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendment 02)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Excessive happiness
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Psychotic episode or disorder
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

SIGNATURES

Authors:

PPD

Date

Eisai Ltd.

PPD

Date

Eisai, Inc.

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added China to the list of regions to participate in the study and changed the number of levels of stratification by region from 6 to 7.	Added to allow enrolment in China	Synopsis • Study Design • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.4.4 Section 9.7.1.6.1
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 1 Section9.5.2.1, Table 2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. . In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/Assessment (Table 2), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 3
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.		
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC (pharmacokinetic) PK parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body-weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 2 and Table 3)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
administrations of the EQ-5D…"		
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 3)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2, Table 4

Revisions to Version 2.0

New version/date: Version 3.0/06 Feb 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of elenbecestat (E2609) from drugs	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	with symptomatic effects.	Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 3

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
mandatory at the second of the follow-up visits.		
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the DSMB for periodic review during the study	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 1 Table 2 Table 3 Table 4
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as	Section 9.2.1

Revisions to Version 1.0

New version/date: Version 2.0/16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	secondary	
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of elenbecestat (E2609) in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 02)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01) V3.0 06 Feb 2017 (Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at

Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory, PD (Aβ(1-x) and other isoforms), biomarker testing, and pharmacogenomics (PGx) analyses of *ApoE* genotype. (revised per Amendments 01 and 02) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 02) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 02)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified

to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata

(PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
    - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
    - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
    - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendments 01 and 02)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat (E2609)
- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 02)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks

before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 02)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Plasma will be collected to measure PD (Aβ1-x) at baseline and various timepoints during treatment and followup. (revised per Amendment 02)

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. (revised per Amendments 01 and 02)

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug).

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendment 02)

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period. (revised per Amendment 01)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured

using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods. Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 02)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 02)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis (revised per Amendment 01)
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog_{14} Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels

- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2)

[yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be

censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be

analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0\text{-}24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation	Term
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization

Abbreviation	Term
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 02)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 02)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat, (E2609) tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the

lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5

metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

Preliminary PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight. Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 02)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI

- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 02)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are: (revised per Amendment 02)

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendments 01 and 02)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All

subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

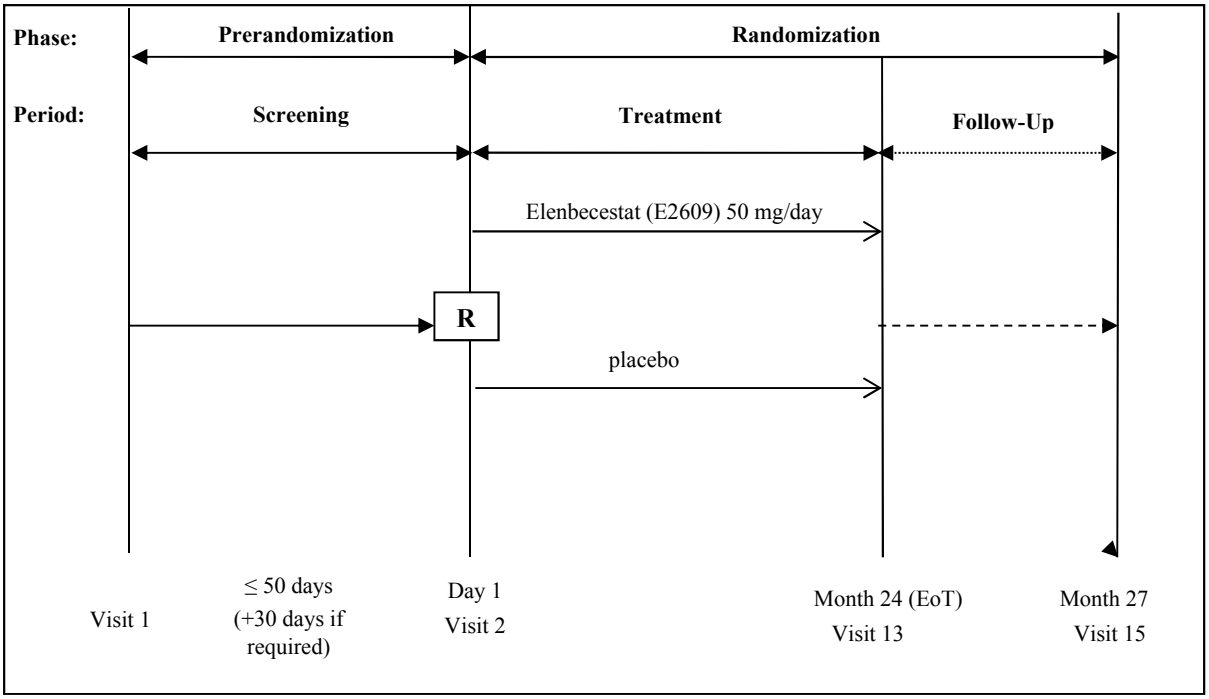

Figure 1 Study Design for E2609-G000-301

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF

substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 02): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarker assays, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 02)

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 02) Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score

using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. (revised per Amendment 01)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by elenbecestat (E2609) increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the

selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 01)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendment 02)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02) Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendments 01 and 02)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

- Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 02)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

- any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat (E2609)

- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects who develop moderate or severe hepatic impairment during the study must discontinue study drug. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on these results elenbecestat (E2609) 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) and this, in turn, should translate into greater clinical benefit while minimizing the safety concerns. Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendments 01 and 02)

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 02)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 02)

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 02)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 02)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 02). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 02)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word List Learning Immediate and Delayed Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For this task, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the total number of words recalled during all 3 trials. The total number of words recalled ranges from 0-30. This task is given at the beginning of the ADAS-Cog$_{14}$. At the end of the ADAS-Cog$_{14}$, the subject is asked to recall as many words as possible from the previously studied list. The total number of words recalled on this Delayed Recall task ranges from 0-10.

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in

Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods required at screening to determine subject eligibility for the study. Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples

will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Biomarkers

The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity.

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD assessments as specified in Table 2 and Table 3. The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples and CSF (if applicable) collected at Screening will be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 2 and Table 3. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01)

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis

- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia; ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 2) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils) Prothrombin time and INR (derived from prothrombin time) are to be performed for all subjects as part of Screening (revised per Amendment 02). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 02)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing. (revised per Amendment 01) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells (revised per Amendment 01)

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 02)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive suicidality assessment on the clinical assessment of suicidality will trigger a C-SSRS to be administered. A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the

study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, thyroid function, vitamin B12[h]	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and other biomarkers[j]	X (Tier 3)
Blood sample for immunologic assessments, including isolation of PBMCs for storage and later testing	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD baseline)[n,o,p]	X (Tier 5)

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 02)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time and INR derived from the prothrombin time are to be performed as part of Screening. (revised per Amendment 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP.

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 02). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure.

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendments 01 and 02)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and later testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and other biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[x]												X	X			

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes:

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie., at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendments 01 and 02) (revised per Amendments 01 and 02)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). (revised per Amendment 01) Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 02)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 02)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if

no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED). (revised per Amendment 01)

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 02)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that might indicate signals of possible drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire); categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3. (revised per Amendments 02)

[aa] The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

Table 4 Summary of Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points x Volume per Collection (mL)		Total Volume[a] (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry	15	1×5 mL	14×5 mL	75 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	5 mL
Viral screen at Screening (Hepatitis B and C)	1	1×5 mL	None	5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.)	1	None	1 x 4 mL	4 mL
Vitamin B12 at Screening	1	1×5mL	None	5 mL
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendment 01)	15	1×20 mL	14×20mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample (revised per Amendment 02)	10	1×24 mL	9×12 mL	132 mL
PK analysis (revised per Amendment 02)	7	none	7×4 mL	28 mL
Pharmacogenomic sample	1	1×3 mL	None	3 mL
All blood samples, total volume collected (revised per Amendment 02)		69 mL	558 mL	627 mL
CSF				
Amyloid eligibility	1	1×12 mL	None	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic.

a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit).

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their

last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is

planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI (revised per Amendment 01)
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendments 01 and 02) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendment 01) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate,

randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 01)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, , prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to

be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic or Ocular Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendment 02)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 02)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 02)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 02)
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Excessive happiness
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Psychotic episode or disorder
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

SIGNATURES

Authors:

PPD

Eisai Ltd.

Date

PPD

Eisai, Inc.

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 02)
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 1.0

New version/date: Version 2.0 / 16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Randomization will be stratified according to **region**, disease status, and use of concomitant medications. Randomization will no longer be stratified by *ApoE* genotype.	To avoid bias in the subjects randomized in different regions. A*po*E genotype was removed as a stratification factor because further review of available data suggested that this is not an important factor in disease progression such that it will be unlikely for there to be an interaction of A*po*E genotype with treatment effect.	Synopsis • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Analyses for Primary Efficacy Endpoints Section 9.1 Section 9.2.4 Section 9.3 Section 9.4.4 Section 9.5.1.4.2 Section 9.7.1.6.1
ECG recordings will be evaluated by a central reader.	For consistency	Synopsis • Conduct of the Core Study • Safety Assessments Section 9.1.2.1 Section 9.5.1.5 Section 9.5.1.5.6
Added a secondary objective that E2609 is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD.	Introduction of an objective - cognitive/memory test as a separate secondary endpoint for the study	Synopsis • Objectives • Study Endpoint Section 8.2 Section 9.7.1.1.2 Section 9.2.1 Section 9.2.3 Section 10
Added a secondary objective to determine whether E2609 is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)	To provide a further assessment of disease modification 3 months post 24 months of treatment. This will aid differentiation of E2609 from drugs with symptomatic effects.	Synopsis • Objectives • Secondary Endpoints • Analysis for Secondary Efficacy Endpoints Section 8.2 Section 9.7.1.1.2

Revisions to Version 1.0

New version/date: Version 2.0 / 16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
		Section 9.7.1.6.2
The term "total lymphocyte count" was changed to "absolute lymphocyte count".	To provide complete clarity that the test will reflect the absolute count from the hematology and differential panel rather than the calculated count for lymphocytes	Synopsis • Safety Assessments • Exclusion Criteria Section 9.3.2 Section 9.3.3
Additional instructions provided regarding temporary suspension of study drug following lymphocytopenia and subsequent rechallenge.	To ensure a consistent approach to testing of absolute lymphocyte count upon rechallenge of study drug following temporary suspension due to lymphocytopenia	Synopsis • Safety Assessments Section 9.3.3
The Modified Hachinski Scale will be administered in Tier 1 instead of Tier 2.	To identify those subjects with vascular dementia and exclude them earlier in the screening process	Synopsis • Conduct of the Core Study Section 9.1.1.1.1 Section 9.1.1.1.2 Section 9.5.2.1
Addition of sleep/dream questionnaire for subjects reporting AEs of abnormal dreams, nightmares or sleep terrors.	To collect more details on the nature, frequency, and impact of any abnormal dream, nightmare, or sleep terror AE	Synopsis • Safety Assessments Section 9.5.1.5 Section 9.5.2.1 Section 9.7.1.8
Requirement to measure absolute lymphocyte count every 4 weeks for subjects who have a Grade 2 or greater lymphocytopenia during the follow-up period. Clinical chemistry and hematology test made mandatory at the second of the follow-up visits.	To follow any Grade 2 or greater lymphocytopenias that occur post-study drug on a regular basis through to resolution or confirmation of a non drug-related cause of the lymphocytopenia	Section 9.5.1.5.2 Table 3
Clarification regarding testing of blood samples for immunological assessments.	Some of the immunological assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of immunological assessments will be provided to the	Section 9.1.1.1.3 Section 9.1.2.1 Section 9.5.1.5 Table 1 Table 2

Revisions to Version 1.0

New version/date: Version 2.0 / 16 Nov 2016 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
	DSMB for periodic review during the study	Table 3 Table 4
The term "live vaccines" was changed to "live vaccines / live attenuated vaccines".	For additional clarity that live attenuated vaccines are also excluded from this study	Synopsis • Exclusion Criteria Section 9.3.2 Appendix 12, Listing 3
Malignant neoplasms within **5** years of Screening are excluded from the study (changed from 3 years).	Correction	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that subjects who are illiterate are also excluded from participation in the study.	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
The following text "If the subject has reached the clinical stage of dementia, the site clinician will also be required to confirm the severity of dementia" and the text "and assessment of dementia severity" has been deleted.	Staging of disease will focus on dementia and nondementia rather than severity of dementia	Synopsis • Conduct of the Core Study Section 9.1.2.1 Section 9.5.2.1
"Secondary" was replaced with "biomarker".	Biomarker objectives are not defined in the protocol as secondary	Section 9.2.1
Additional blood samples for PD evaluation will be drawn at follow up.	To assess the continuous effect of E2609 in blood biomarkers after study drug discontinuation	Section 9.5.2.1
EudraCT Number was added.	Per template	• Title Page • Protocol Signature Page • Investigator Signature Page

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E2609
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol) V2.0 16 Nov 2016 (Amendment 01)
IND Number:	109308
EudraCT Number:	2016-003928-23
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether E2609 is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population pharmacokinetics (PK) of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI (revised per Amendment 01)
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning

task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (6 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 6 levels of the region are:

1. North America
2. Western Europe (including Oceana region)
3. Eastern Europe
4. Japan
5. Other Asian countries
6. South America

(revised per Amendment 01)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale. (revised per Amendment 01)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these

assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility. (revised per Amendment 01)

Following these initial assessments, blood will be collected from all subjects for clinical laboratory and biomarker testing and pharmacogenomics (PGx) analyses of *ApoE* genotype. (revised per Amendment 01) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of childbearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol.

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). (revised per Amendment 01) This staging decision will be verified via a central review process and adjudicated if necessary

(adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, and centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need

not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)
2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

- Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3)
9. Results of laboratory tests conducted during screening that are outside the following limits:
   - Absolute lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher) (revised per Amendment 01)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - E2609
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with

study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of E2609 concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug).

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

All subjects will have *ApoE* genotyping performed. (revised per Amendment 01)

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period. (revised per Amendment 01)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods.

Plasma concentrations of E2609 that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant PD biomarkers will be measured in the blood samples collected at times that match the PK draws.

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis (revised per Amendment 01)
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months (revised per Amendment 01)

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently

complied with the protocol.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [6 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendment 01) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start

only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at

24 months

- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be explored

through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard

deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
AST	aspartate aminotransferase
AUC	area under the concentration x time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
Bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	childbearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid

Abbreviation	Term
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	Electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	Identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task

Abbreviation	Term
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood monocyte (count)
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	Randomization
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TB	Tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	Unscheduled
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (E2609 Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of E2609. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 E2609 program, and is primarily designed to evaluate the efficacy, safety, and tolerability of E2609 in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 8 Phase 1 studies and 1 Phase 2 study:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo-and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of E2609 on QTc interval in healthy subjects (thorough QT study). Two dose levels of E2609 were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of E2609 in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

The Phase 1 study, Study E2609-A001-101 (Study 101) has been completed. This study was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults

aged 50 to 85 with subjective memory complaints and who qualified as having MCI or mild AD.

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild

increase (by approximately 70%) of the area under the concentration x time curve (AUC) of E2609. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Based on these results, it is not considered necessary to impose restrictions during E2609 treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between E2609 and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of E2609 up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of E2609. The effects of E2609 on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg E2609. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the E2609 plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of E2609 were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of

TEAEs. There were no AEs of special interest or viral infections. There were no effects of E2609 on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of E2609 doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the E2609 concentrations and QTcF effect was similar between Japanese and white subjects at the E2609 dose of 50 mg.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD (revised per Amendment 01)
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD (revised per Amendment 01)
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months (revised per Amendment 01)
- To evaluate the population PK of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al, 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al. 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (6 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 6 levels of the region are:

1. North America
2. Western Europe (including Oceana region)
3. Eastern Europe
4. Japan
5. Other Asian countries
6. South America

(revised per Amendment 01)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild

AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

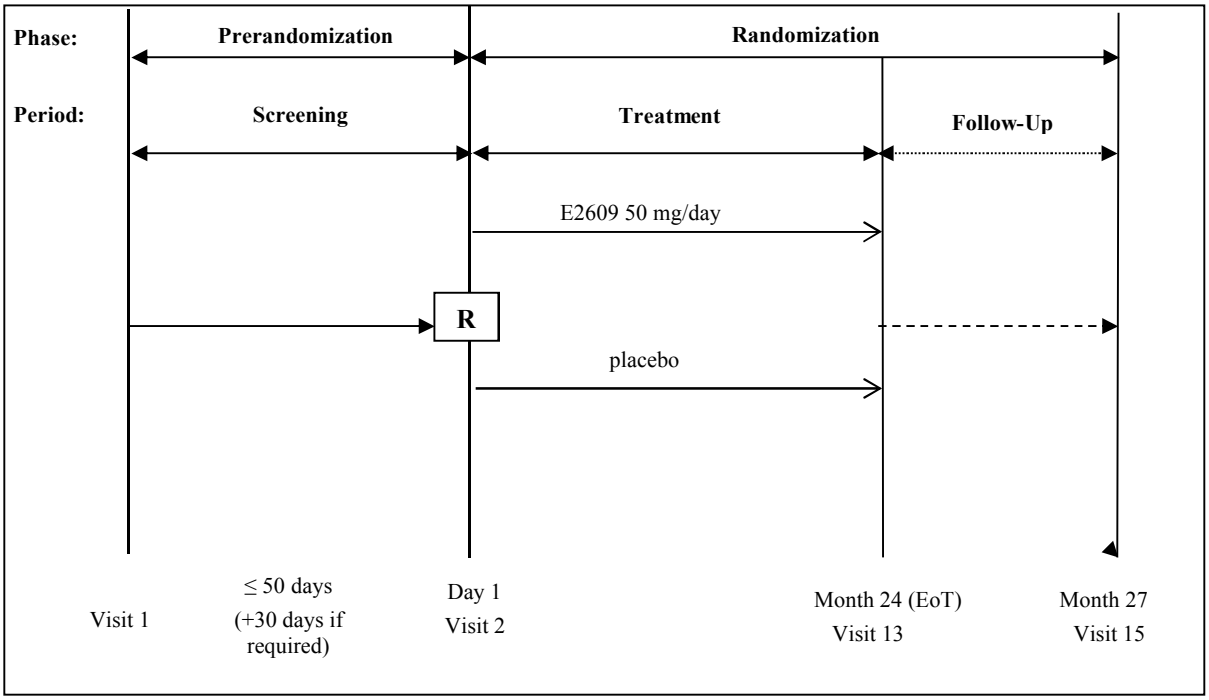

Figure 1 Study Design for E2609-G000-301

E2609 = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. (revised per Amendment 01) The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified

via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), and the following quality of life assessments: (revised per Amendment 01)

- EQ-5D: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarker assays, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility

MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result).

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. (revised per Amendment 01) These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01) The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical

laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood monocytes (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). (revised per Amendment 01)

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. (revised per Amendment 01) Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day E2609) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of E2609 compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their

premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of E2609 compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. (revised per Amendment 01)

Additional important biomarker endpoints will evaluate the AD modifying properties of E2609 by assessing several human AD biomarkers. (revised per Amendment 01) Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of E2609 on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by E2609 has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by E2609 increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as E2609. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow

disease progression with E2609 are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included. (revised per Amendment 01)

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects.

(revised per Amendment 01)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of E2609 on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of E2609 on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (6 levels), , clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild

dementia due to AD, and concurrent AD medication use. (revised per Amendment 01)Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute

illness has completely resolved, even if the concomitant medication continues. (revised per Amendment 01)

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. (revised per Amendment 01) Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age

group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or International Normalized Ratio [INR] >3)

9. Results of laboratory tests conducted during screening that are outside the following limits:

- Absolute lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher) (revised per Amendment 01)

- Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

- Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine/live attenuated vaccine in the 3 months before randomization (revised per Amendment 01)

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

- Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments

- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately (revised per Amendment 01)

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded. (revised per Amendment 01)

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - E2609

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject’s discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is E2609 and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the E2609 arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry

N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At

enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of E2609 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day. Based on these results E2609 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) and this, in turn, should translate into greater clinical benefit while minimizing the safety concerns. Based on these data, E2609 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (6 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. (revised per Amendment 01)

9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the

code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. (revised per Amendment 01) Concomitant medications (including benzodiazepines and opiates) which

are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number

- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required in the US) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation

procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). (revised per Amendment 01) A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word List Learning Immediate and Delayed Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al, 1989), (cited by Mohs et al, 1997). For this task, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the total number of words recalled during all 3 trials. The total number of words recalled ranges from 0-30. This task is given at the beginning of the ADAS-Cog$_{14}$. At the end of the ADAS-Cog$_{14}$, the subject is asked to recall as many words as possible from the previously studied list. The total number of words recalled on this Delayed Recall task ranges from 0-10.

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake.

Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods required at screening to determine subject eligibility for the study. Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR testing should be performed for subjects who consent to provide a CSF sample and who have a medical condition with bleeding risk that is not under adequate control. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after

completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Biomarkers

The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity.

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD assessments as specified in Table 2 and Table 3. The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples and CSF (if applicable) collected at Screening will be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety. (revised per Amendment 01)

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01) Blood samples for immunologic assessments will be collected as outlined in Table 2 and Table 3 Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. (revised per Amendment 01)

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic

edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have absolute lymphocyte count measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing. (revised per Amendment 01) Cerebrospinal fluid sampling NOTE: INR testing should be performed for subjects who consent to provide a CSF sample and who have a medical condition with bleeding risk that is not under adequate control. (revised per Amendment 01)

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMC = peripheral blood monocyte count. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. (revised per Amendment 01) At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy

will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). (revised per Amendment 01) During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 01)

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit,

the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of childbearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive suicidality assessment on the clinical assessment of suicidality will trigger a C-SSRS to be administered. A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, thyroid function, vitamin B12[h]	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and exploratory biomarkers[j]	X (Tier 3)
Blood sample for immunologic assessments, including isolation of PBMCs for storage and later testing	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD baseline)[n,o,p]	X (Tier 5)

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood monocyte count, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. (revised per Amendment 01) Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

e: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine.

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP.

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of childbearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. CSF collection should always precede amyloid PET, and the 2 assessments should be separated by at least 24 hours. A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, CSF collection should always precede amyloid PET, and the 2 assessments should be separated by at least 24 hours. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) are excluded from CSF collection. (revised per Amendment 01)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and later testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[x]												X	X			

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/dream questionnaire[y]																X
Randomization	X															
Dispense study drug	X[z]	X	X	X	X	X	X	X	X	X	X					

Notes for Table 3

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie., at either Visit 14 or Visit 15) should have absolute lymphocyte count measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. (revised per Amendment 01)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). (revised per Amendment 01) Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR

or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

o Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s). (revised per Amendment 01)

p The clinical assessment of suicidality will require input from both the subject and the study partner

q There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

r There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner

s MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

u Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

v Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

w PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, it is recommended that samples be collected at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED). (revised per Amendment 01)

x For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) are excluded from CSF collection.(revised per Amendment 01)

y Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. (revised per Amendment 01)

z The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

Table 4 Summary of Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points x Volume per Collection (mL)		Total Volume (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry	15	1×5 mL	14×5 mL	75 mL
Serum pregnancy test at Screening (females of childbearing potential only)	1	can use blood drawn for clinical chemistry	None	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	None	5 mL
Viral screen at Screening (Hepatitis B and C)	1	1×5 mL	None	5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.)	1	None	1 x 4 mL	4 mL
Vitamin B12 at Screening	1	1×5mL	None	5 mL
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendment 01)	15	1×20 mL	14×20mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample	8	1×20 mL	7×12 mL	104 mL
PK analysis	8	1×4 mL	7×4 mL	32 mL
Pharmacogenomic sample	1	1×3 mL	None	3 mL
All blood samples, total volume collected		69 mL	534 mL	603 mL
CSF				
Amyloid eligibility	1	1×12 mL	None	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMC = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their

last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is

planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) (revised per Amendment 01)
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months (revised per Amendment 01)

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI (revised per Amendment 01)
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD). (revised per Amendment 01)

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [6 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. (revised per Amendment 01) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 01)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint,

will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendment 01) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be

explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 01)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of

exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, , prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD). (revised per Amendment 01)

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to

be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization Until the Last Treatment Visit

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline Until the Last Treatment Visit

Systemic Immunosuppressants[a] and Immunoglobulin therapy	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization Until the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Excessive happiness
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Psychotic episode or disorder
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2609-G000-301

Study Protocol Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigational Product Name: E2609

IND Number: 109308

EudraCT Number: 2016-003928-23

SIGNATURES

Authors:

PPD

Eisai Ltd.

Date

PPD

Eisai, Inc.

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	E2609
IND Number:	109308
EudraCT Number:	2016-003928-23

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E2609
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 26 Aug 2016 (original protocol)
IND Number:	109308
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Phase 3

Objectives

Primary Objective

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], volumetric

Magnetic Resonance Imaging [vMRI]) at 24 months

- To evaluate the population pharmacokinetics (PK) of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by Amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity as measured by task free functional MRI (fMRI)
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objective(s)

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to Apolipoprotein E (*ApoE*) genotype, concurrent AD medication use, and

clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD.

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using Amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task.

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the modified Hachinski scale and on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory and biomarker testing and pharmacogenomics (PGx) analyses of *ApoE* status. Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of childbearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the

respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either Amyloid PET (Screening Amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening Amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the Amyloid PET and CSF longitudinal substudies respectively. Subjects who complete Amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional Amyloid PET and/or CSF assessments as indicated in the protocol.

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). If the subject has reached the clinical stage of dementia the site clinician will also be required to confirm the severity of the dementia. This staging decision and assessment of dementia severity will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the Amyloid PET longitudinal substudy, Amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject

has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, and ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on

the ISLT.

4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

      NOTE: Subjects may undergo both the Amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to Amyloid PET or CSF for eligibility purposes are not required to participate in the Amyloid PET or CSF longitudinal substudies. Use of a historical Amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the Amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as an anti-infective, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:

- total abstinence (if it is their preferred and usual lifestyle)
- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count less than 50,000 or INR greater than 3)

9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Total lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
    - Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma in

situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - E2609
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization.

Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of E2609 concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical Amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the Amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal Amyloid PET or CSF or both substudies will also receive Amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug).

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

All subjects will have *ApoE* genotyping performed and randomization will be stratified according to *ApoE4* status.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period.

Total lymphocyte count will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of total lymphocytes. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks. Restart of study drug may take place only when total lymphocyte count returns to greater than LLN.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months . HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau,

p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods.

Plasma concentrations of E2609 that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant PD biomarkers will be measured in the blood samples collected at times that match the PK draws.

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months, eg the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken.
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months

Biomarkers Endpoints

- Change from baseline in Amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline on the CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, *APOE4* status [positive, negative], concurrent AD medication use at randomization (Visit 2) [yes, no], clinical dementia [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple

imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (Amyloid PET, CSF t-tau and p-tau, vMRI, fMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus

placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in Amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be

larger than that from this observation study.
Sample Size Rationale The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
AST	aspartate aminotransferase
AUC	area under the concentration x time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	childbearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid

Abbreviation	Term
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system

Abbreviation	Term
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood monocyte (count)
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis

Abbreviation	Term
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal sub-study will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and Amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is Alzheimer's disease) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (E2609 Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of E2609. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-301 (Study 301), is 1 of 2 studies in the Phase 3 E2609 program, and is primarily designed to evaluate the efficacy, safety, and tolerability of E2609 in subjects with EAD. Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to Alzheimer's disease or Mild Alzheimer's disease. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 8 Phase 1 studies and 1 Phase 2 study:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of E2609 on QTc interval in healthy subjects (thorough QT study). Two dose levels of E2609 were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of E2609 in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

The Phase 1 study, Study E2609-A001-101 (Study 101) has been completed. This study was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults

aged 50 to 85 with subjective memory complaints and who qualified as having MCI or mild AD.

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild

increase (by approximately 70%) of the area under the concentration x time curve (AUC) of E2609. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Based on these results, it is not considered necessary to impose restrictions during E2609 treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between E2609 and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of E2609 up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of E2609. The effects of E2609 on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg E2609. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the E2609 plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of E2609 were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of

TEAEs. There were no AEs of special interest or viral infections. There were no effects of E2609 on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of E2609 doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the E2609 concentrations and QTcF effect was similar between Japanese and white subjects at the E2609 dose of 50 mg.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

8.2 Secondary Objectives

The secondary objectives of this study are

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], volumetric Magnetic Resonance Imaging [vMRI]) at 24 months
- To evaluate the population PK of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by Amyloid PET in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI

- To evaluate whether E2609 is superior to placebo in preserving connectivity as measured by task free functional MRI (fMRI)
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al, 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al. 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to Apolipoprotein E (*ApoE*) genotype, concurrent AD medication use, and clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD.

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using Amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

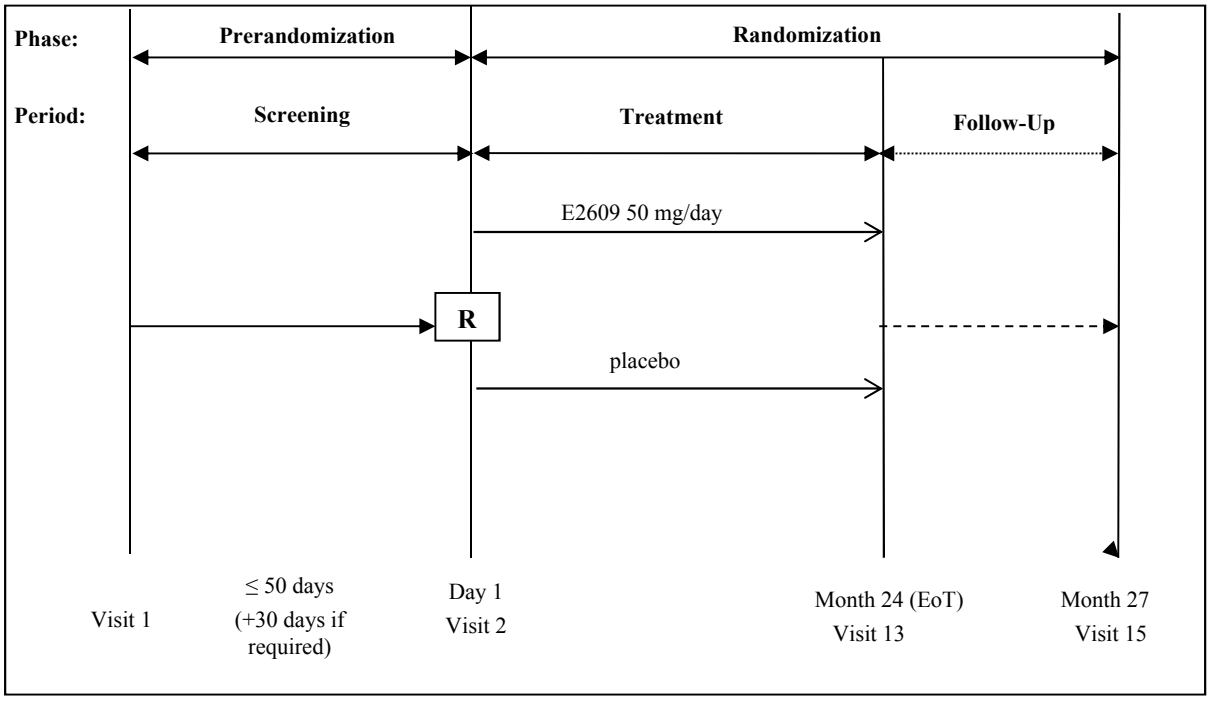

Figure 1 Study Design for E2609-G000-301

E2609 = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an Amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS), the modified Hachinski ischemic scale, and the following quality of life assessments:

- EQ-5D: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, and exploratory biomarker assays, and for isolation of peripheral blood monocytes (PBMCs). A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either Amyloid PET (Screening Amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of

amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result).

Screening Amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the Amyloid PET and CSF longitudinal substudies respectively. Subjects who complete Amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the Amyloid PET and/or CSF longitudinal substudies will undertake additional Amyloid PET and/or CSF assessments as indicated in the protocol. (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the subject will complete the following assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken and stored for isolation of PBMCs and for future assessment of immune status if required. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to

stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). If the subject has reached the clinical stage of dementia the site clinician will also be required to confirm the severity of the dementia. This staging decision and assessment of dementia severity will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and isolation of PBMCs for storage, and a urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the Amyloid PET longitudinal substudy, Amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day E2609) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of E2609 compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a

cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of E2609 compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$, MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important secondary endpoints will evaluate the AD modifying properties of E2609 by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of E2609 on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by E2609 has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by E2609 increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as E2609. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with E2609 are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by Amyloid PET in subjects with EAD

- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

CSF biomarkers and Amyloid PET assessments on disease progression at 24 months (and at 12 months for Amyloid PET) will be evaluated in a sub-study of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with baseline levels of *ApoE4* genotyping in

addition to the baseline imaging variables to help explain differences in treatment response between subjects.

The study will be stratified for *ApoE4* gene status in order to account for any *ApoE*-status-by-treatment interaction.

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of E2609 on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal sub-study.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of E2609 on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free functional resting state MRI (fMRI) can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps (based on critical anatomical regions, eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to *ApoE* genotype, concurrent AD medication use, and clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the Amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to Amyloid PET or CSF for eligibility purposes are not required to participate in the Amyloid PET or CSF longitudinal substudies. Use of a historical Amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the Amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as an anti-infective, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be

willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count less than 50,000 or INR greater than 3)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Total lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

- Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments

- Severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 3 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 3 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - E2609

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects From Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Total lymphocyte count will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of total lymphocytes. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks. Restart of study drug may take place only when total lymphocyte count returns to greater than LLN.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is E2609 and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the E2609 arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of E2609 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day. Based on these results E2609 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) and this, in turn, should translate into greater clinical benefit while minimizing the safety concerns. Based on these data, E2609 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to *ApoE* genotype, concurrent AD

medication use, and clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD.

9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required in the US) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog_{14} are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping

center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007).

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free functional resting state MRI (fMRI) can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps (based on critical anatomical regions, eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is one of the two methods required at screening to determine subject eligibility for the study. Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal sub-study will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED).

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Biomarkers

The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity.

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD assessments as specified in Table 2 and Table 3. The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples and CSF (if applicable) collected at Screening will be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype (homozygous or heterozygous) of subjects enrolled in this study. The findings will be used for stratification purposes and also in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An Amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional sub-study, longitudinal Amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal Amyloid PET imaging will only be conducted on subjects that have consented to this optional sub-study and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. PBMCs and blood samples for immunologic status will be collected as outlined in Table 2 and Table 3 for exploratory immunomodulatory and immune-based analyses. These samples will be frozen and stored.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic

edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet one of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood sample for PBMCs and for immunological status for storage for subsequent testing of immune status Cerebrospinal fluid sampling

CMV = cytomegalovirus, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, PBMC = peripheral blood monocyte count.

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method.

Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

Neurologic Examination

A full neurologic examination will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of childbearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive suicidality assessment on the clinical assessment of suicidality will trigger a C-SSRS to be administered. A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Modified Hachinski ischemic scale	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, thyroid function, vitamin B12[h]	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and exploratory biomarkers[j]	X (Tier 3)
Blood sample for isolation of PBMCs	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD baseline)[n,o]	X (Tier 5)

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-301: Prerandomization Phase

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood monocyte count, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an Amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

e: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine.

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP.

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of childbearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. CSF collection should always precede Amyloid PET, and the 2 assessments should be separated by at least 24 hours. A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the Amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, CSF collection should always precede Amyloid PET, and the 2 assessments should be separated by at least 24 hours. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood samples for isolation of PBMCs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI_{10}	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional sub-study)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[w]		X	X		X	X		X		X		X	X			
CSF sampling for PK and PD (optional sub-study)[x]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-301

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Randomization	X															
Dispense study drug	X[y]	X	X	X	X	X	X	X	X	X	X					

Notes for Table 3

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period.

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the

Notes for Table 3

functional ability of the subject among other factors.

o Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. If the subject has progressed into clinical dementia the site clinician will confirm the severity of the dementia. In addition, the site clinician is required to confirm the staging of the disease for subjects who, at Screening, were clinically staged as in the early stages of mild dementia due to AD, does the subject still meet the definition of the early stages of mild dementia due to AD or have they progressed into a more severe stage of dementia due to AD. This staging decision and assessment of dementia severity will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

p The clinical assessment of suicidality will require input from both the subject and the study partner

q There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

r There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner

s MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t PET scanning (if subject has consented to optional sub-study) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

u Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

v Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

w PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and they should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day.

x For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months.

y The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

Table 4 Summary of Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points x Volume per Collection (mL)		Total Volume (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry	15	1×5 mL	14×5 mL	75 mL
Serum pregnancy test at Screening (females of childbearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	None	5 mL
Viral screen at Screening (Hepatitis B and C)	1	1×5 mL	None	5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.)	1	None	1 x 4 mL	4 mL
Vitamin B12 at Screening	1	1×5mL	None	5 mL
Blood for PBMC isolation	15	1×20 mL	14×20mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample	8	1×20 mL	7×12 mL	104 mL
PK analysis	8	1×4 mL	7×4 mL	32 mL
Pharmacogenomic sample	1	1×3 mL	None	3 mL
All blood samples, total volume collected		69 mL	534 mL	603 mL
CSF				
Amyloid eligibility	1	1×12 mL	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMC = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of

SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see

Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT(S)

The primary endpoint of the study is

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINT(S)

The secondary endpoints of the study are

- Time to worsening of CDR scores by 24 months, eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken.
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINT(S)

The exploratory endpoints of the study are

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are

- Change from baseline in Amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months

- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized

according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline on the CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, *APOE4* status [positive, negative], concurrent AD medication use at randomization (Visit 2) [yes, no], clinical dementia [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model

the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to

dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (Amyloid PET, CSF t-tau and p-tau, vMRI) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in Amyloid PET SUVR composite at 24 months for brain amyloid levels

- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: *ApoE4* status (positive or negative), prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will

also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog_{14}, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an

estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-301 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization Until the Last Treatment Visit

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline

Systemic Immunosuppressants[a] and Immunoglobulin therapy	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live Vaccines Within 3 Months Before Randomization Until the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being
		Excessive happiness

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis
		Psychotic episode or disorder

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2609-G000-301

Study Protocol Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigational Product Name: E2609

IND Number: 109308

SIGNATURES

Authors:

PPD

Date

Eisai Ltd.

PPD

Date

Eisai, Inc.

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-301
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	E2609
IND Number:	109308

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 6.0

New version/date: Version 7.0/23 May 2019 (per Amendment 06)

Change	Rationale	Affected Protocol Sections
Added that subjects in Japan who lose the capacity to provide informed consent during the Core Study may be eligible for inclusion in the Extension Phase if the investigators obtain subject assent and consent of the legal representative	To comply with applicable professional standards and local laws/regulations	Synopsis • Inclusion Criteria – Extension Phase Section 5.3 Appendix 5 in Section 12

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Added details for the open-label Extension Phase	As indicated in the original protocol the Extension Phase details are included	Synopsis • Study Period and Phase of Development • Study Design • Objectives • Study Treatments • Inclusion Criteria • Duration of Treatment • Concomitant Drug/ Therapy • Assessments • Bioanalytical Methods • Statistical Methods Section 5.3 Section 9.1 Figure 1 Section 9.1.3 Section 9.1.3.1 Section 9.1.4 Table 5 Appendix 5 in Section 12
Pooling of study 301 and 302 analysis, with decreased subjects	Sample size re-estimation indicated the requirement for	Synopsis • Site(s)

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
and sites in each study	1900 subjects compared with the original 1330 subjects per study. Studies will be combined to achieve the required numbers.	• Core Study Objectives • Study Design • Number of Subjects • Statistical Methods Section 6 Section 8.1 Section 8.2 Section 9.1 Section 9.2.1 Section 9.3 Section 9.7.1.1 Section 9.7.2
Study 202 summary of safety and efficacy added and its Extension Phase, exposure	Emerging clinical data indicating acceptable safety and signals of clinical efficacy	Section 7.1 Section 9.4.4
Key secondary objectives defined	Three key secondary objectives have been defined from the multiple secondary objectives, indicating those of most importance that will be tested in a hierarchical manner if the primary objective is significant.	Synopsis • Core Study Objectives • Statistical Methods Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added Alzheimer's Disease Composite Score (ADCOMS) as a secondary objective for the Core Study	This novel endpoint has been included, aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.	Synopsis • Core Study Objectives, Secondary Objectives • Assessments • Study Endpoints Section 8.2 Section 9.2.1 Section 9.2.3 Section 9.5.1.3.1 Section 9.7.1.1.2 Section 9.7.1.6.2
Added of CDR-SB and ADCOMS enriched by baseline amyloid PET SUVR as a secondary objective for the Core Study	Elenbecestat may be more effective when amyloid reaches a minimum level but before too much is on board	Synopsis • Core Study Objectives, • Study Endpoints Section 8.2 Section 9.7.1.1.2

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
		Section 9.7.1.6.2
Added a biomarker objective and endpoints for the Core Study	Clarification	Synopsis • Core Study Objectives • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 8.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Revised country list	To reflect that South Africa is a participating country	Synopsis • Study Design Section 9.1
Added that if subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator	To clarify that subjects would not need to withdraw from study	Synopsis • Study Design Section 9.1.2.1 Section 9.5.1.5.7
Added that CSF will be used to assess PD, PK, and exploratory biomarkers.	Clarification	Synopsis • Study Design Section 9.1.2.1
Added that CSF and PET assessments should be conducted before any other visit assessments and while the subject is still study drug	Clarification	Synopsis • Study Design Section 9.1.2 Section 9.1.2.1
Added that new AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation	Clarification	Synopsis • Study Design Section 9.3.3
Historical cerebrospinal fluid (CSF) samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF	Allows historical CSF sample to be analyzed to determine eligibility	Synopsis • Inclusion Criteria • Assessments Section 9.3.1

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
amyloid positivity		
Added that levels of Vitamin B12 may be confirmed with methylmalonic acid analysis, if available	For flexibility on Vitamin B12 deficiency analysis	Synopsis • Exclusion Criteria Section 9.3.2 Table 3 Section 9.5.2.2 Table 6
Revised exclusion criterion (#14) regarding a prolonged QTc interval calculated using Fridericia's formula (QTcF) was changed to clarify that if the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed.	Machine read QTcF values might be lower than central reads. Subjects are SF if the average of 3 ECGs on central read > 450 ms. Instructing sites to perform triplicate ECGs when machine reads are > 440 ms will ensure all required evaluations are completed.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.6 Table 5
Revised exclusion criterion (#19) to clarify that subjects who participated in a clinical study that involved a new chemical entity or investigational drug for Alzheimer's Disease (AD) are to be excluded	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
Added events of possible abuse potential to the safety assessments for the Core Study and Extension Phase	Clarification	Synopsis • Assessments Section 9.7.1.8
Revised text to clarify that if a Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice during the Treatment Period, that is confirmed on repeat testing and within a 6-month period, then the subject should be discontinued permanently from the study drug in the Core Study.	To clarify that this applies to Treatment Period in the Core Study.	Synopsis • Assessments Section 9.3.3
Added timepoints when the NPI-10 item will be conducted in the Extension Phase	Wording added	Synopsis • Assessments

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Clarified that *ApoE4* status may be included in the model if appropriate	Clarification	Synopsis • Efficacy Analyses Section 9.7.1.6.1 Section 9.7.1.6.2
Revised Core Study analysis of biomarker endpoints to clarify that change from baseline in functional magnetic resonance imaging (fMRI) parameters as appropriate, will be determined	Clarification	Synopsis • Analysis of Biomarker Endpoints Section 9.7.1.7.3
Added that a futility analysis is planned when approximately 30% of subjects have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date	Clarification	Synopsis • Interim Analyses Section 9.7.3
Clarified that subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will need to provide separate Extension Phase-specific written informed consent	Clarification	Section 5
Added a valid period for assessment results of Tiers 1 to 5	Clarification	Section 9.1.1.1
Added information to permanent discontinuation	Clarification to cover subjects where the study drug had been temporary suspended for more than 3 weeks	Section 9.3.3
Added that termination of therapy for symptomatic treatment of AD during the study should be undertaken in compliance with local standard of care.	Clarification	Section 9.4.7
Added information on CSF sampling at Visit 13 (early discontinuation [ED])	Clarification to avoid samples being taken when subject has been off the study drug for more than 7 days.	Section 9.5.1.3.3
Revised to clarify that postdose pharmacokinetic (PK) samples will not be needed for subjects who are	To clarify requirements for collection of PK samples when subjects are not being dosed.	Section 9.5.1.4.1

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
temporary suspended from study drug or permanently stopped the study drug at the ED visit		
Added neurogranin as an Exploratory Biomarker Subset	Correction	Table 2
Added details as to when amyloid positron emission tomography (PET) and tau PET imaging will be conducted	Clarification	Section 9.5.1.4.2
Added how adverse events (AEs) will be handled for subjects who permanently discontinue study drug, but continue in the study.	Wording added	Section 9.3.3 Section 9.5.1.5.1
Added treatment changes in depigmentation/hypopigmentation/ vitiligo/loss of hair color to the list of AEs that will require the collection of information to provide detailed description of the event	AE of interest added	Section 9.5.1.5.1
Revised blood sampling for immunological assessments and added corresponding footnote	Based on Data Safety Monitoring Board recommendation	Table 5 Table 6
Revised the example of the locally approved amyloid-imaging agent to Neuraceq	To reflect main imaging agent in use during the study	Table 4 Table 5
Added a footnote to state that Visit 2 bottles of study drug will be redispensed at Visit 3	Clarification	Table 5
Added footnotes to state when initiation, termination or change in dose is permitted or that herbal medications and preparations should be discussed with the medical monitor	Clarification	Listing 4 in Section 12
Revised list of permitted medication and permitted medication if used for short-term basis	Clarification	Listing 5 in Section 12

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Added footnote that herbal medications or preparations should be discussed with the medical monitor and benzodiazepines were deleted	Clarification	Listing 5 and Listing 6 in Section 12
An editorial revision was made to remove "(E2609)"; grammatical, typographical, and formatting changes were also made	Correction	Throughout

Revisions to Version 4.0

New version/date: Version 5.0/19 Jul 2018 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) who have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 4 Table 5 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 5)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 4 and Table 5)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 5)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 5)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion criteria

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
		Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 5) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis – Statistical Methods • Bioanalytical Methods Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 4)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 5)
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 2)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 4)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 6)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result documentation from the urine	Added for clarification	Section 11.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted “pharmacogenomics (PGx)” data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Added new study director	To establish separate study directors in the 2 identical Phase 3 studies	PROTOCOL SIGNATURE PAGE
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4(new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSF collection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4 and Table 5) Section
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4
Revised text for amyloid CSF	Revised for clarification	Section 9.5.1.3.3

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
sampling to note that 2 methods are available rather than required		Section 9.5.1.5 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the medical monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14)	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for assessments; added clarification that the volumes are estimates and may vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 6
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) $\geq$ 1.7; bilirubin $\geq$ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 4), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening.	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 4

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 5

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
by the white blood cell count × percentage of lymphocytes.		
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the Treatment Period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 4, and Table 5)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4, and Table 5)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"		
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 5)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 6)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat (E2609)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01) V3.0 04 Apr 2017 (Amendment 02) V4.0 28 Jun 2017 (Amendment 03) V5.0 19 Jul 2018 (Amendment 04) V6.0 21 Jan 2019 (Amendment 05) V7.0 23 May 2019 (Amendment 06)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Approximately 250 global sites (revised per Amendment 05)

Study Period and Phase of Development

This Phase 3 study will consist of:

- Core Study: The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow up.
- Open-label Extension Phase: Up to 24 months of additional treatment, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first, and 1-month follow up. (revised per Amendment 05)

Core Study Objectives

Primary Objective

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD) pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 05)

Key Secondary Objectives (revised per Amendment 05)

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-302

Other Secondary Objectives (revised per Amendment 05)

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the

CDR-SB at 24 months for subjects with EAD enriched by baseline PET standardized uptake value ratio (SUVR) pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale – cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] amyloid beta [Aβ] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 05)
- To explore potential plasma and CSF biomarkers of Alzheimer's disease (AD)

(eg, neurofilament light [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 (YKL-40), and neurogranin [Ng]) (revised per Amendment 05)To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)

- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

Exploratory Objectives

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    - EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    - Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Extension Phase Objectives (revised per Amendment 05)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with EAD

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia, for subjects who were not clinically staged as having dementia at Core Study baseline, based on a clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is

maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by PET (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using vMRI
- To evaluate the long term-effect of elenbecestat in preserving brain connectivity as measured by task-free fMRI
- To evaluate the long-term effect of elenbecestat on CSF tau, p-tau, and Aβ levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, Ng)

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other AD pharmacotherapies
- To explore the long-term effect of elenbecestat on the NPI-10 and if available NPI-12

Study Design

The study consists of a Core Study followed by an open-label Extension Phase. The Core Study is a 24-month treatment with 3-month follow up, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 05)

Study E2609-G000-301 and Study E2609-G000-302 will be combined with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 05)

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries

7. South America

(revised per Amendment 05)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET, tau PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. . (revised per Amendments 04 and 05)

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. . The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 02 and 05).

Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 04) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, ISLT, and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

For any given subject, every effort should be made to ensure that the diagnosing clinician

(responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01 and 03) Vital signs and weight will be recorded, and a single 12-lead ECG will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities that may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task-free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both. (revised per Amendment 03) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies, respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 01 and 04)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug and is not within 3 months of a previous CSF sample). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug. (revised per Amendment 04 and 05)Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24-month

Treatment Period. (revised per Amendment 03)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 03) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 05) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 05)

Extension Phase

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

During the Extension Phase, the assessment of safety will include the recording of all AEs. In addition, vital signs, weight, safety blood and urine laboratory tests, ECGs [no central reading of ECGs], suicidality, neurological examination, NPI, and signals of abuse potential will continue to be assessed.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study) and at Visit 24/ ED, but will be abbreviated for all other timepoints.

Clinical assessments will be performed every 4 months (MMSE, FAQ) or 12 months (CDR, ADAS-cog14). Blood biomarkers and MRI will be assessed every 12 months. Optional amyloid and

tau PET and CSF biomarker assessments will be conducted at the end of 2-year open-label treatment (Extension Phase).

Subjects who complete treatment in the Extension Phase are required to complete the Follow-up Visit 1 month after the last dose.

Subjects may discontinue the open-label study drug for any reason, but will be required to complete the ED Visit (within 7 days of last dose) and the Follow-up Visit 1 month after the last dose of study drug. In addition, subjects are required to discontinue study drug if any of the criteria specified in Section 9.3.3 are met. (revised per Amendment 05)

Number of Subjects

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 05)

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

Core Study

1. MCI due to AD or mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment(eg, tau:Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 03 and 05).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a

stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications that are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

Extension Phase (revised per Amendment 05)

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 06)
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

Core Study

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

Females of child-bearing potential who:

- Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
  - total abstinence (if it is their preferred and usual lifestyle)
  - an intrauterine device or intrauterine hormone-releasing system
  - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
  - have a vasectomized partner with confirmed azoospermia.
- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as

defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 03 and 05)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)
9. Results of laboratory tests conducted during Screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below LLN or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 05)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment,

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 03)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled

steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03). If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 05)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 05)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before

randomization

20. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Extension Phase

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food. (revised per Amendment 05)

Duration of Treatment

Core Study: The maximum estimated duration for each subject is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow-up).

Extension Phase: The estimated duration for a subject is 25 months (ie, 24 months of treatment and 1-month follow-up. (revised per Amendment 05).

Concomitant Drug/Therapy (both Core Study and Extension Phase) The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 01)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 01 and 03)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 02 and 05) Subjects who start on AChEI or memantine or change their

dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 03 and 05)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments (both Core Study and Extension Phase)

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD. ADCOMS (Wang, et al., 2016) is a composite clinical score that represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, of the MMSE, the CDR, and the ADAS-cog14. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change. (revised per Amendment 05)

Pharmacokinetic Assessments (Core Study Only)

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (both Core Study and Extension Phase)

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, and 03)

Blood will be collected to measure PD and biomarkers in both the Core Study and the Extension

Phase. (revised per Amendments 02, 03, and 05)

Amyloid PET imaging or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 03) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. Historical CSF samples may be analyzed to confirm amyloid pathology, if collected, processed, and stored under appropriate conditions and approved by the sponsor. (revised per Amendments 03 and 05)

Subjects who consent to participate in the amyloid and tau PET longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED visit in the Core Study and at 24 months or at the ED visit in the Extension Phase. (revised per Amendments 03, 04, and 05)

Subjects who consent to the CSF substudy will have samples taken at 24 months or at the ED visit in both the Core Study and Extension Phase for PD and biomarker assessments. (revised per Amendments 02 and 05)

Safety Assessments (both Core Study and Extension Phase)

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings (evaluated by a central reader in the Core Study); physical, dermatologic, and neurologic examinations; assessment of suicidality, events of possible signals of drug abuse potential, and MRIs during the Treatment Period. (revised per Amendments 01 and 05)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6-month period during the Core Study treatment, then the subject should be discontinued permanently from the study drug in the Core Study. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period, then the subject should be discontinued permanently from the study drug. (revised per Amendments 01, 03, and 05).

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study

partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly until month 3 of treatment in the Core Study and until Month 2 in the Extension Phase. Thereafter, they will be monitored every 3 months in the Core Study and every 4 months in the Extension Phase until the end of the Treatment Period and at Follow-up Visits. (revised per Amendment 05)

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period in the Core Study and during the Extension Phase will require a more detailed follow-up. (revised per Amendments 03 and 05)

Other Assessments (Core Study Only)

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Other Assessments (Extension Phase Only)

The NPI-10 or if available NPI-12 will be conducted at Day 1, Month 4, Month 12, and then every 12 months. If the NPI-12 questionnaire is used, both NPI-10 and NPI-12 scores will be calculated. (revised per Amendment 05)

Bioanalytical Methods (both Core Study and Extension Phase)

CSF AD assessment (eg, tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits. (revised per Amendment 03) Exploratory biomarkers such as neurofilament NFL, Ng, YKL-40, and VILIP1 may also be measured using validated assays. (revised per Amendments 01 and 05)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 03)

Plasma concentrations of elenbecestat that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 05)

Core Study

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 05)

Key Secondary Endpoints (revised per Amendment 05)

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

Other Secondary Endpoints (revised per Amendment 05)

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies

Biomarker Endpoints

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in plasma amyloid biomarker eg, Aβ(1-x) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)
- Change from baseline in total hippocampal volume at 24 months using vMRI

- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from

baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 05)

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 05)

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie., any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 05)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between eg, 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. *ApoE4* status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Time to worsening of a CDR score

is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendments 04 and 05)

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 05)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of

Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure

parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 05)

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Extension Phase (revised per Amendment 05)

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
    - Brain amyloid and tau PET levels
    - Total hippocampal volume as measured by vMRI
    - fMRI parameters as appropriate
    - CSF t-tau, p-tau and amyloid beta (Aβ(1-42)) levels
    - Plasma and CSF amyloid beta (Aβ(1-x))
    - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
    - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

Extension Phase Analysis Sets

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase,

which include: Safety, FAS, PPS and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive an increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al, 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, the MMRM model will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET SUVR
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline in Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints. The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined

2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at the time of the futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 05)

Sample Size Rationale

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]) is selected to estimate the mean and standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group, which are 1.5 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 05)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCOMS	Alzheimer's Disease Composite Score
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval

Abbreviation	Term
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	early Alzheimer's disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata

Abbreviation	Term
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SUVR	standardized uptake value ratio
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 03) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 03) The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative, impartial witness, study partner). (revised per Amendment 03) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 04)

Subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will be asked to provide separate Extension Phase-specific written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (as determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 06)

At the start of the Extension Phase, an assessment of capacity to consent should be undertaken, and continue periodically throughout the Extension Phase treatment, utilizing the method and frequency as for the Core Study above. (revised per Amendment 05)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 250 investigational sites globally. (revised per Amendment 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ-secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat Investigator's Brochure). Another study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat was administered orally by gavage once a day to male rats for 28 days before, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 03) Further details of the nonclinical data to date with elenbecestat can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing to assess the PK levels of elenbecestat and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open-label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat. It also investigated the effects of elenbecestat on the PK properties of digoxin. (revise per Amendment 03)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open-label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat. (revised per Amendment 01)

Study E2609-G000-202 (Study 202) has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat given daily, along with safety and exploratory efficacy. Elenbecestat was generally well tolerated; no unexpected safety concerns emerged. Although sample sizes were small, statistically significant decreases in PET standardized uptake value ratios (SUVR) were seen. Clinical assessments suggest elenbecestat may have attenuating effects on cognitive decline in MCI-to-moderate AD subjects (Lynch, et al., 2018). Forty-three out of the 70 randomized subjects completed the study and of these 41 elected to enroll in an open-label Extension Phase. The Extension Phase has been running for 2 years and currently has 36 subjects still receiving elenbecestat. (revised per Amendment 05)

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat. In elderly subjects treated with 50 mg of elenbecestat, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects that were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or ECG parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of

latent infections in subjects who received single doses of elenbecestat. A single dose of elenbecestat up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the Treatment Period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat when coadministered with elenbecestat but not when dosed at least 2 hours apart from elenbecestat. Elenbecestat (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat. Based on these results, it is not considered necessary to impose restrictions during elenbecestat treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications that are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when elenbecestat will not be present, as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study

confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat. The effects of elenbecestat on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50-mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat PK parameters (C_{max} and AUC). (revised per Amendments 01 and 03) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the Core Study is:

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 05)

8.2 Secondary Objectives

The key secondary objectives of the Core Study are as follows (revised per Amendment 05):

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-302

The other secondary objectives of the Core Study are as follows (revised per Amendment 05):

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of CDR scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline

based on a clinical diagnosis evaluated every 3 months pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale – cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF amyloid beta [Aβ], total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], and functional MRI [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the population PK of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 05)
- To explore potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL), visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin (Ng) (revised per Amendment 05)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI

- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD, as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

8.3 Exploratory Objectives

The exploratory objectives of the Core Study are:

- To explore the relationship between elenbecestat exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

For objectives specific to the Extension Phase, refer to Appendix 5 in Section 12.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group Core Study with an open-label Extension Phase in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list-learning task (ISLT). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 05)

Study E2609-G000-301 and Study E2609-G000-302 will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study.

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendment 05)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendments 04 and 05)

The maximum estimated duration for each subject in the Core Study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase, and a 3-month follow-up).

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase. (revised per Amendment 05)

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related

to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. (revised per Amendment 05) The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

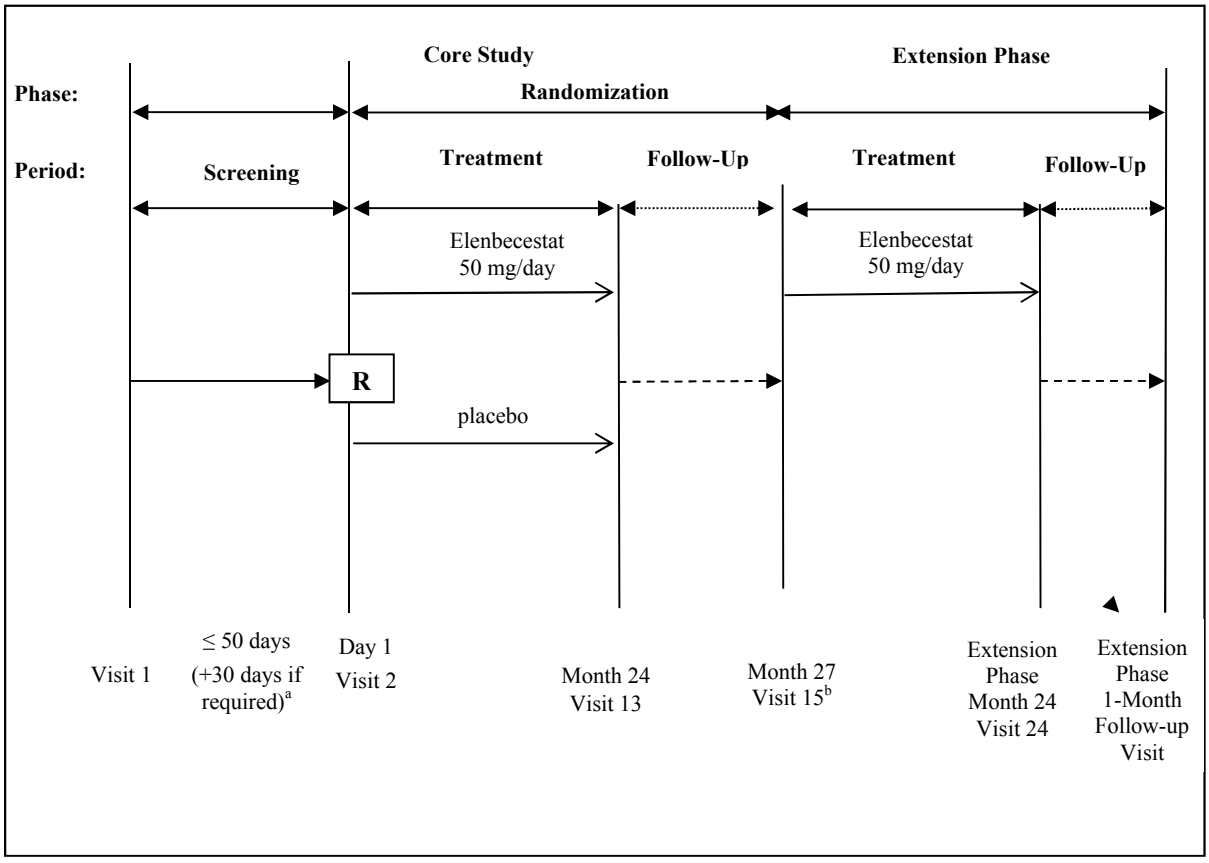

Figure 1 Study Design for E2609-G000-302 (revised per Amendment 05)

Elenbecestat = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a: Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

b: The last day of the Core Study (Visit 15) is also the first day of the Extension Phase

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional

longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained before the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5, (ie during the Randomization Phase of the study). Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 03, and 04)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of Screening. (revised per Amendment 04)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Subjects may be re-screened, if deemed appropriate by the investigator and medical monitor. Unless otherwise stated, results of the following will be valid over the timeframes stated below: (revised per Amendment 05)

- Tiers 1 to 3 Screening will be valid for 96 days from the date of assessment
- Tier 4 MRIs will be valid for 90 days from the date of assessment

- Tier 5 CSF results and amyloid PET scans will be valid for 90 days from the date of assessment, while historical amyloid PET scans will be valid for 12 months

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, (ISLT, CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, before the CDR is administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 03)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue

confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 02 and 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities that may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment or both. (revised per Amendment 03) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for lumbar puncture (LP) to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 03) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy); the tau PET scan

must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. (revised per Amendment 05) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the LP. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of assessment for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 03) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 03 and 04)

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24-month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must

be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 01, 03, and 04) CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug. (Refer to Table 5 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.) (revised per Amendment 05)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03) Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as needed. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 05) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication (revised per Amendment 03). Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED Visit/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD, and assessment of immune status are performed at different intervals throughout the Treatment Period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug (revised per Amendments 01, 03, 04, and 05). Please refer to Schedule of Assessments (Table 5).

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-up Period.

In some cases, UNS visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment on study drug and the 3-month follow up in the Core Study. The open-label Extension Phase will continue for 24 months, or until commercial availability of elenbecestat, or until a positive benefit-risk assessment in this indication is not demonstrated, whichever comes first (See Appendix 5 for full details of the Extension Phase) (revised per Amendments 02 and 05)

9.1.3.1 Extension Phase Follow-Up Period (revised per Amendment 05)

All subjects, regardless of whether they complete all 24 months of open-label treatment or discontinue study drug prematurely, will complete a post-treatment Follow-up Visit 1 month after the last dose of open-label study drug.

In some cases, UNS visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments in Appendix 5) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.4 End of Study

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 02 and 05)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

Study E2609-G000-301 and Study E2609-G000-302 are multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group studies in subjects with EAD including MCI due to AD and the early stages of mild AD. The 2 studies will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study across 2 treatment groups, (placebo, 50 mg per day elenbecestat) for 24 months. (revised per Amendment 05) The maximum estimated duration for each subject on study is

anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month Follow-up Period).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog14 (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. A novel composite endpoint, ADCOMS (Wang, et al., 2016), is also included as a secondary endpoint. (revised per Amendment 05)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 03)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes

(eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). Therefore, attempts to slow disease progression with elenbecestat are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog14 immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical

meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

ADCOMS is a weighted linear combination of 12 items from 3 of the above clinical scales, the ADAS-cog, the MMSE, and the CDR. These 12 items consist of the predictive variables A4, A7, A8, A11, M1, M7, C1, C2, C3, C4, C5, and C6. The names of these items and the corresponding scale names are described in Table 1. Data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412 and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.

Table 1 Predictive Variables for the ADCOMS

Scale	Item ID	Item Name	PLS weight
ADAS-cog	A4	Delayed Word Recall	0.00847483
	A7	Orientation	0.017088
	A8	Word Recognition	0.003732761
	A11	Word Finding	0.016211
MMSE	M1	Orientation Time	0.041567
	M7	Drawing	0.038238
CDR	C1	Personal Care	0.054321
	C2	Community Affairs	0.1091
	C3	Home and Hobbies	0.089039
	C4	Judgment and Problem Solving	0.069493
	C5	Memory	0.058724
	C6	Orientation	0.078152

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale, CDR = Clinical Dementia Rating, ID = identification, MMSE = Mini Mental State Examination, PLS = Partial Least Squares.

(revised per Amendment 05)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat treatment.

9.2.4 Rationale for Biomarkers

CSF biomarkers, amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a LP procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 04)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ[1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 03)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 03) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 04)

Tau PET imaging will be performed to evaluate the effects of elenbecestat on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who

have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

vMRI and fMRI
vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason, hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers
Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as NFL, Ng, VILIP1, or YKL-40) become available. (revised per Amendments 01, 02, and 05)

9.3 Selection of Study Population

At least 850 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 250 centers worldwide. (revised per Amendment 05) Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau: Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 03 and 05).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up

information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

For inclusion criteria specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically

(ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 03 and 05).
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)
9. Results of laboratory tests conducted during Screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and

calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

- Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
- Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 05)

10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 03)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:

- Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
- Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTcF interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 05)
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 05)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery that requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion

if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments (Table 5) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6 month period, during the Core Study Treatment Period, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period then the subject should also be discontinued permanently from study drug (revised per Amendments 01, 03, and 05).

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 01 and 02) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 02)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the

medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 02)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

For subjects who temporarily suspend study drug (eg, ALC $<800/mm^3$) but progress to permanently discontinue study drug, the ED and Follow-up Visits should be scheduled as follows: (revised per Amendment 05)

- If ≥ 3 weeks since the last study dose, then the ED Visit should be scheduled immediately, and the 1-month Follow-up Visit will not be required
- If <3 weeks since the last study dose, then the ED visit should be scheduled immediately, and Follow-up Visits at 1 and 3 months after the last dose will be required

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to

return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications.. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 05) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

Core Study For this study, the test drug is elenbecestat and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 5 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the Treatment Period, the investigator should discuss with the medical monitor whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

For details on treatment to be administered in the Extension Phase, refer to Appendix 5 in Section 12.

9.4.2 Identity of Investigational Product(s)

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat

- Test drug code: E2609
- Generic name: elenbecestat
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained

within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) along with safety and exploratory efficacy of 5, 15, and 50 mg of elenbecestat given daily. Based on the PK/PD modeling results, elenbecestat 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 02) Based on these data, elenbecestat 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and

sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 01)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 01 and 03)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before

randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD (revised per Amendment 02 and 05). Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 4 and Table 5. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 Psychometric Assessments

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment, and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog14: The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-cog14 that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-cog14. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0 to 10. (revised per Amendment 02)

ADCOMS: ADCOMS is a composite score of 12 items from the CDR, MMSE, and ADAS-cog, and does not require any additional assessments. (revised per Amendment 05)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative

measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 4 and Table 5, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7 to 10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available at screening to determine subject eligibility for the study. (revised per Amendment 02) Subjects who undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal.

CSF samples at Visit 13 should be collected while the subject is still on the study drug and before the other visit assessments. All ED CSF samples need to be taken no later than 7 days after the last dose of study drug. All CSF samples should be taken at approximately the same time of day as at the Screening Visit. (revised per Amendment 05)

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to the CSF procedure at Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat. Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 03) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 4 and Table 5. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporary suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose PK samples are not required. (revised per Amendment 05)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 2 lists PD, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 03)

Table 2 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (revised per Amendment 05)

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Example of Exploratory Biomarkers	PD	Example of Exploratory Biomarkers
Whole Blood/ Plasma	ApoE [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) Aβ42/Aβ40 ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 Tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)

a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 02 and 03)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 02 and 03)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 4 and Table 5. (revised per Amendment 02) The blood sample collected for PD analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 03)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the

event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 02 and 03) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 03) The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

For subjects participating in the amyloid PET substudy, amyloid PET imaging will be conducted on separate days from the scheduled visits and should be conducted before the clinic Visit 9 and no later than 7 days after the last dose for Visit 13/ED. (revised per Amendment 05)

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 04)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

For subjects participating in the tau PET substudy, tau PET imaging will be conducted on separate days from the scheduled visits and should be conducted before clinic Visit 13/ED and no later than 7 days after the last dose of study drug. (revised per Amendment 05)

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities that will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 04)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 4 and Table 5); and MRIs as detailed in Table 4 and Table 5. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 4 and Table 5. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs that will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 05)

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF until 4 weeks post last dose, and followed up for 12 weeks, or until resolution, whichever comes first (as shown in Table 5). Adverse events relating to study procedures will be collected until the end of study participation. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. (revised per Amendment 05)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog14, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form during the Treatment Period and first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). (revised per Amendment 03).

Euphoria-related terms: (revised per Amendment 03)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 03)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 03)

- Somnolence (revised per Amendment 03)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 03)

- Psychosis
- Aggression (revised per Amendment 03)
- Confusion and disorientation (revised per Amendment 03)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 03)

- Drug tolerance
- Habituation (revised per Amendment 03)
- Substance related disorders (revised per Amendment 03)

Physical dependence or withdraw (only for events observed within 14 days of the last dose of study drug): (revised per Amendment 03)

- Drug withdrawal syndrome (revised per Amendment 03)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the medical monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); treatment-emergent depigmentation/ hypopigmentation/vitiligo/loss of hair color; amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality (revised per Amendments 02 and 05).

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related)	A causal relationship between the study drug and the AE is a reasonable possibility.
No (not related)	A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)

- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. Table 4 and Table 5 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time) and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 01 and 02). A prothrombin time and INR should also be performed before LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 (with reflex MMA if available for low vitamin B12) (revised per Amendment 05) Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing if required. (revised per Amendments 02 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, MMA = methylmalonic acid, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 4 and Table 5 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 5. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 4 and Table 5. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 02) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 5 and will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 4 and Table 5. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least

5 minutes. If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 05).

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 4 and Table 5. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 5).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 4 and Table 5, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?" (revised per Amendment 02) A positive suicidality assessment from the subject or their study partner on the clinical

assessment of suicidality will trigger the C-SSRS to be administered (revised per Amendment 02). A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the medical monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 5 presents the schedule of procedures/assessments for the Randomization Phase.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendment 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendment 02)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 02)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 04)	X (Tier 5)

NOTES:

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	Prerandomization
Period	Screening
Visit	1
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 03 and 04)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QTcF = QTc interval calculated using Fridericia's formula, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study). (revised per Amendment 04)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, before the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR derived from the prothrombin time, and aPTT are to be performed as part of Screening (revised per Amendments 01 and 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 03) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 02)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	Prerandomization
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	

subject identification number. (revised per Amendment 03)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Neuraceq, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 90 days from the date of the original screening procedure. (revised per Amendments 04 and 05)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 2 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendments 04 and 05).

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Consent (subject and study partner)															X[dd]	
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X														X[dd]	
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (revised per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, (revised per Amendment 02) [ee]	X	X	X	X	X	X	X	X								
PBMCs for storage and testing required (revised per Amendment 05)	X					X		X				X	X			
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X[dd]	X

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog14[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI-10	X					X		X		X		X	X		X[hh]	
C-SSRS	X	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X	X		X[dd]	
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X[ii]	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X		X[cc]	
Tau PET (optional substudy) [u]												X	X		X[cc]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[y]												X	X		X[cc]	
Adverse events[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[bb]	X	X	X	X	X	X	X	X	X	X				X[dd]	

Notes

ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, QTcF = QTc interval calculated using Fridericia's formula, UNS = unscheduled, vMRI = volumetric MRI.

a: A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visits 7 to 13 inclusive (including for subjects who discontinue study drug early but who return for clinical assessments at 12 and 24 months). These windows should be calculated from Day 1. A window of ±3 days calculated from the last dose will be permitted for the Follow-up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog14) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-up Visits (Visit 14 and Visit 15).

c: All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Visit 15 will also act as Baseline for subjects who successfully complete the Core Study and will be enrolled into the open-label Extension Phase. (revised per Amendments 01 and 05)

d: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15 or if the subject is continuing in the Extension Phase.

f: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

g: A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED) and Visit 15 if entering the Extension Phase (revised per Amendment 05). Neurologic examinations at the other visits will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h: Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i: Single 12-lead standard ECGs will be recorded. If the QTcF machine read is greater than 440 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values. (revised per Amendment 05)

j: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k: More frequent testing may be required per local regulations. (revised per Amendment 03) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m: Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 03)

n: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

o: Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

p: The clinical assessment of suicidality will require input from both the subject and the study partner

q: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

r: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

s: MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the medical monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t: Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuraceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 03 and 04)

u: For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 04)

v: Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w: Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

PK samples are not required.

x: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 02 and 03)

y: For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

z: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

aa: AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 01 and 03)

bb: The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03) Visit 2 bottles are re-dispensed at Visit 3 after accountability is performed. (revised per Amendment 05)

cc: Only for Extension Phase subjects who did not participate in optional longitudinal substudies in the Core Study but who wish to consent to optional longitudinal substudies in the Extension Phase.

dd: For subjects entering the Extension Phase only.

ee: Immunological assessments only required for subjects randomized before 07 Sep 2018ff: New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, AEs relating to study procedures will be collected only

gg: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

hh: For those subjects entering the Extension Phase, NPI-12 will be used if available and both NPI-10 and NPI-12 scores calculated.

ii: Not required for those entering Extension Phase

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 4 and Table 5 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 4). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 6 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 02) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 02)

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 02 and 03)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 03)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 02 and 03)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 02)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 02 and 03)	1	none	1×3.5 mL	none	3.5 mL

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening and MMA where available (revised per Amendments 02, 03, and 05)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, (revised per Amendments 03 and 05)[b]	8		1×10 mL	7×10 mL	80 mL
Blood for PBMCs (revised per Amendment 05)	4	none	1×10 mL	3×10 mL	40 mL
Blood for immune status (revised per Amendment 03)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 01, 02, and 03)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendment 02)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendments 01 and 02)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 01, 02, 03, and 05)		25.8 mL	46.8 mL	298.9 mL	371.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit) ; actual volume may vary based on local regulations. (revised per Amendment 02)
b: Immunological assessment samples not required for subjects randomized after 07 Sep 2018 - reducing total blood volume to 291.5 mL (revised per Amendment 05)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 4 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. (revised per Amendment 05)

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 03)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 03)

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (ocular herpes, new onset seizures, and symptomatic cerebral vasogenic edema), as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 5 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

For statistical methods specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 05)

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 05)

9.7.1.1.2 SECONDARY ENDPOINTS

The key secondary endpoints of the study are as follows (revised per Amendment 05):

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

The other secondary endpoints of the study are as follows (revised per Amendment 05):

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies

- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies

9.7.1.1.3 BIOMARKER ENDPOINTS

The biomarker endpoints of the study are:

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.1.4 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.

- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog14, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization [Visit 2] [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at

24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 05)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 05):

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 05)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. ApoE4 status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-x), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 03, 04, and 05) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, with treatment group and randomization stratification variables, as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05)

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship

will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 05)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 05)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 03)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog14, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 05)

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined two studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor

may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 05)

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter. (revised per Amendment 05)

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation))
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 01 and 03)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 03)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Initiation, termination or change in dose is permitted if in line with local standard of care. Any changes are required to be stable for 4 weeks before any cognitive assessments.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of cognitive enhancements then they should follow the same rules as the medications in this listing. (revised per Amendment 05)

Listing 5 Medications Permitted if Used on PRN or Short Term Basis (2 to 4 Weeks) Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Benzodiazepines (revised per Amendments 03 and 05)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Sedatives	
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	

PRN = Pro re nata

This list is not exhaustive.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of negative effects on cognition, they should follow the same rules as the medications in this listing. (revised per Amendment 05)

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 03)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 03)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts

Categories (revised per Amendment 03)			**Examples**[a]	
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 03)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 03)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	

Categories (revised per Amendment 03)			**Examples**[a]	
(revised per Amendment 03)	**17**	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 03)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 03)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 03)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 03)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 03) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

Appendix 5 Open-label Extension Phase (revised per Amendment 05)

Primary Objective

- To assess the long-term safety and tolerability of daily dosing with elenbecestat in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on Clinical Dementia Rating –Sum Of Boxes (CDR-SB), Alzheimer's Disease Composite Score (ADCOMS), Mini Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14), and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia for subjects who were not clinically staged as having dementia at Core Study baseline, based on clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by positron emission tomography (PET) (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using volumetric magnetic resonance imaging (vMRI)
- To evaluate the long-term effect of elenbecestat in preserving brain connectivity as measured by task-free functional magnetic resonance imaging (fMRI)
- To evaluate the long-term effect of elenbecestat on CSF t-tau, p-tau, and amyloid beta (Aβ) levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL),visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin [Ng])

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other Alzheimer's disease (AD) pharmacotherapies
- To explore the long-term effect of elenbecestat on the Neuropsychiatric Inventory (NPI)-10 and if available NPI-12

Eligibility Criteria

Subjects who do not meet all of the inclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up period (Visit 15) of the Core Study and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). In Japan, if a subject loses the capacity to consent, in the investigator's opinion during the course of the Core Study, the subject's assent should be obtained (if required in accordance with local laws, regulations, and customs) along with the written informed consent of a legal representative. (revised per Amendment 06)
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Study Design and Plan

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 24 months (2 years), or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first.

Subjects who are enrolled and complete the Core Study, including the 3-month follow-up period, will have the option to participate in the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects may enter the Extension Phase immediately following the completion of Core Study Visit 15. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. For all subjects, assessments performed at Visit 15 may serve as baseline values for the Extension Phase.

Subjects may discontinue from the open-label study drug for any reason but are required to complete the Early Discontinuation (ED) Visit (within 7 days of last dose). In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3 (Removal of Subjects from Therapy or Assessment) are met.

Subjects who complete the Extension Phase treatment, or discontinue the study drug are required to complete the Follow-up Visit, 1 month after their last dose. The study will end when the last subject has completed the last Extension Phase study visit.

Treatment

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food.

Assessments

Assessments will be conducted as shown in Table 5 Visit 15 (Day 1 of the Extension Phase) and as shown in Table 9 for all other Extension Phase visits following the guidelines as indicated for the Core Study in Section 9.5. Concomitant therapy is allowed as stated in Section 9.4.7 and treatment compliance and accountability will be performed as indicated in Section 9.4.8 and Section 9.4.9, respectively.

Safety assessments (physical examinations, neurological examinations, vital signs, safety laboratory tests, ECGs [no central reading of ECGs], signals of potential abuse, pregnancy test for females of child-bearing potential, Columbia Suicide Severity Rating Scale (C-SSRS), and assessment of suicidal thinking/behavior, immunological assessments, safety magnetic resonance imaging (MRI) will be monitored according to Table 9 and all adverse events (AEs) and serious adverse events (SAEs) recorded.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study), and Visit 24/ED, but will be abbreviated for all other timepoints.

Safety laboratory blood tests will be collected as indicated in Table 9 and analyzed by a central laboratory.

Blood samples for pharmacodynamic (PD) and biomarker analyses (Table 7) will be collected as indicated in Table 9. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Subjects that have consented to the optional CSF substudy (either at the start of the Core Study or Extension Phase) will have samples taken as indicated in the Table of Assessments to analyze PD and biomarkers (Table 7). Longitudinal CSF sample is taken before other Visit 24 assessments and whilst subject is still on study drug; for ED, CSF should be taken no longer than 7 days after the last dose.

Safety brain MRI, vMRI, and fMRI assessments will be performed at the end of the Extension Phase Treatment Period (Visit 24 or ED). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be conducted centrally. If subjects have non-MRI compatible devices fitted during Extension Phase

treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator.

Table 7 Extension Phase Samples

Sample	PD	AD Biomarkers	Example of Exploratory Biomarkers
Blood	Aβ(1-x)		Tau NFL VILIP1 YKL-40
CSF		Aβ(1-42) Tau p-tau	NFL Neurogranin VILIP1 YKL-40

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), CSF = cerebrospinal fluid, NFL = neurofilament light, VILIP1 = visinin like protein 1, YKL 40 = human cartilage glycoprotein-39

Optional amyloid and tau PET assessments will be performed at the end of the Extension Phase Treatment Period before other Visit 24/ED assessments and when subjects are still on the study drug and no more than 7 days after the last dose of study drug. Subjects may consent to participate in the PET substudies at the start of the Extension Phase, for whom an additional assessment will be conducted at Visit 15 (before the first dose of the open-label study drug). PET scan acquisition and interpretation will be conducted centrally.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the start of the Extension Phase and at the end of treatment and a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive answer to any clinical assessment of suicidality question (subject or study partner) requires the C-SSRS to be performed; any positive finding on the C-SSRS requires a psychiatric evaluation to be conducted.

Clinical assessments (MMSE, FAQ, CDR, ADAS-cog14, disease staging, NPI) will be administered as described in the Schedule of Assessments (Table 9) and a central review employed to ensure global standardization. If available the NPI version 12 (NPI-12) questionnaire will be used, but both NPI-10 and NPI-12 scores will be calculated.

The Follow-up Visit will take place at 1 month after the last dose of study drug as described in Table 9. These assessments will also be performed if a subject prematurely discontinues from the Extension Phase.

The number of blood samples and the total volume of blood that will be collected throughout the Extension Phase, are summarized in Table 8.

Table 8 Summary of Sample Volumes

Assessment	Total number of collection time points[a]	Number of time points x volume per collection (mL)	Total volume (mL)
		Extension Phase Treatment and Follow-up Periods	
Blood			
Safety labs	11	11×6.3 mL	69.3 mL
PD & biomarker sample	3	3×6 mL	18 mL
Total volume blood collected			**87.3 mL**
CSF PD and biomarker	2[a]	2×12mL	24 mL

CSF = cerebrospinal fluid, PD = pharmacodynamic
a: For subjects who consented to the CSF substudy in the Core Study, only 1 sample (12ml) is required to be collected

EXTENSION PHASE STATISTICAL METHODS

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia on clinical diagnosis at Core Study baseline, based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12

- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

EXTENSION PHASE ANALYSIS SETS

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, Full Analysis Set (FAS), Per Protocol Analysis Set (PPS), and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia based on clinical diagnosis at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al, 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, a mixed effects model for repeated measures (MMRM) will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET standardized uptake value ratio (SUVR)
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI

- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints.

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Sample Size Rationale

Not applicable.

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since first dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, including respiratory rate[d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[h]	X	X	X	X	X	X	X	X	X	X	X	X
MMSE[i]				X	X	X	X	X	X	X		
FAQ[i]				X	X	X	X	X	X	X		
Disease staging						X			X	X		
12-lead ECG[f]		X		X		X			X	X	X	X
NPI[o]				X		X			X	X		
CDR[i]						X			X	X		
ADAS-cog14[j]						X			X	X		
Neurological examination[e]						X			X	X	X	X
Weight						X			X	X		X
Blood sample for PD & biomarkers[j]						X			X	X		
MRI (safety, volumetric and functional sequences)						X			X	X		
Tau PET (optional substudy)									X	X		
Amyloid PET (optional substudy)									X	X		

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since first dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
CSF sampling for PD & biomarkers (optional substudy)[k]									X	X		
C-SSRS	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X		
Clinical assessment of suicidal thinking and behavior	X	X	X	X	X	X	X	X			X	X
Dispense study drug	X[m]	X	X	X	X	X	X	X				

ADAS-cog = Alzheimer's Disease Assessment Scale - cognitive subscale, AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PET = positron emission tomography, QTcF = QTc interval calculated using Fridericia's formula, UNS = Unscheduled Visit

a: A window of ±3 days will be permitted for Visits 16 and 17. A window of ±7 days will be permitted for Visits 18 and 19. A window of ±10 days will be permitted for Visit 20 to 24 inclusive. These windows should be calculated from Extension Phase Day 1. A window of ±3 days will be permitted for the Follow-up Visit calculated from the last Extension Phase dose.

b: Subjects who permanently discontinue taking study drug before end of treatment will undergo an ED Visit within 7 days of their last dose of study drug. In addition, a Follow-up Visit will be scheduled 4 weeks after the last dose of study drug.

c: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator.

d: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

e: A full neurologic examination will be performed at Visit 24 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs.

f: Single 12-lead standard ECGs will be recorded. If the QTc interval calculated using Fridericia's formula (QTcF) machine read is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

g: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis

h: More frequent testing may be required per local regulations. If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

i: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

j: PD and biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose.

k: For subjects who consent to participate in the CSF longitudinal substudy. Visit 24 (or ED) also includes blood PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by lumbar puncture (LP) between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	Extension											
Period	Treatment[a]									ED[b]	1 Month Follow-Up	UNS[c]
Day in Extension Phase	15	29	57	120	245	365	484	610	729			
Visit	16	17	18	19	20	21	22	23	24			
Weeks elapsed since 1st dose in Extension Phase	2	4	8	17	35	52	69	87	104			
Nominal months elapsed since first dose in Extension Phase	0.5	1	2	4	8	12	16	20	24			
Procedures/Assessments												

receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and International Normalized Ratio (INR) (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures.

l: New AEs to be collected 4 weeks post last dose, and followed-up until resolution, or until 12 weeks post last dose, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected.

m: Visit 15 bottles are re-dispensed at Visit 16 after accountability is performed.

n: C-SSR to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior.

o: NPI-12 will be used if available, and both NPI-10 and NPI-12 scores calculated.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat (E2609)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors (revised per Amendments 03 and 05):

PPD

Neurology Business Group, Eisai Inc. — Date

PPD

Neurology Business Group, Eisai Inc. — Date

PPD

Neurology Business Group, Eisai, Inc. — Date

PPD

Neurology Business Group, Eisai Inc. — Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat (E2609)
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Added details for the open-label Extension Phase	As indicated in the original protocol the Extension Phase details are included	Synopsis • Study Period and Phase of Development • Study Design • Objectives • Study Treatments • Inclusion Criteria • Duration of Treatment • Concomitant Drug/ Therapy • Assessments • Bioanalytical Methods • Statistical Methods Section 5.3 Section 9.1 Figure 1 Section 9.1.3 Section 9.1.3.1 Section 9.1.4 Table 5 Appendix 5 in Section 12
Pooling of study 301 and 302 analysis, with decreased subjects and sites in each study	Sample size re-estimation indicated the requirement for 1900 subjects compared with the original 1330 subjects per study. Studies will be combined to achieve the required numbers.	Synopsis • Site(s) • Core Study Objectives • Study Design • Number of Subjects • Statistical Methods Section 6 Section 8.1 Section 8.2 Section 9.1 Section 9.2.1 Section 9.3 Section 9.7.1.1 Section 9.7.2
Study 202 summary of safety	Emerging clinical data	Section 7.1

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
and efficacy added and its Extension Phase, exposure	indicating acceptable safety and signals of clinical efficacy	Section 9.4.4
Key secondary objectives defined	Three key secondary objectives have been defined from the multiple secondary objectives, indicating those of most importance that will be tested in a hierarchical manner if the primary objective is significant.	Synopsis • Core Study Objectives • Statistical Methods Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added Alzheimer's Disease Composite Score (ADCOMS) as a secondary objective for the Core Study	This novel endpoint has been included, aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.	Synopsis • Core Study Objectives, Secondary Objectives • Assessments • Study Endpoints Section 8.2 Section 9.2.1 Section 9.2.3 Section 9.5.1.3.1 Section 9.7.1.1.2 Section 9.7.1.6.2
Added of CDR-SB and ADCOMS enriched by baseline amyloid PET SUVR as a secondary objective for the Core Study	Elenbecestat may be more effective when amyloid reaches a minimum level but before too much is on board	Synopsis • Core Study Objectives, • Study Endpoints Section 8.2 Section 9.7.1.1.2 Section 9.7.1.6.2
Added a biomarker objective and endpoints for the Core Study	Clarification	Synopsis • Core Study Objectives • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 8.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Revised country list	To reflect that South Africa is a participating country	Synopsis • Study Design Section 9.1
Added that if subjects have	To clarify that subjects would	Synopsis

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator	not need to withdraw from study	• Study Design Section 9.1.2.1 Section 9.5.1.5.7
Added that CSF will be used to assess PD, PK, and exploratory biomarkers.	Clarification	Synopsis • Study Design Section 9.1.2.1
Added that CSF and PET assessments should be conducted before any other visit assessments and while the subject is still study drug	Clarification	Synopsis • Study Design Section 9.1.2 Section 9.1.2.1
Added that new AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation	Clarification	Synopsis • Study Design Section 9.3.3
Historical cerebrospinal fluid (CSF) samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity	Allows historical CSF sample to be analyzed to determine eligibility	Synopsis • Inclusion Criteria • Assessments Section 9.3.1
Added that levels of Vitamin B12 may be confirmed with methylmalonic acid analysis, if available	For flexibility on Vitamin B12 deficiency analysis	Synopsis • Exclusion Criteria Section 9.3.2 Table 3 Section 9.5.2.2 Table 6

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Revised exclusion criterion (#14) regarding a prolonged QTc interval calculated using Fridericia's formula (QTcF) was changed to clarify that if the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12 lead ECGs will be performed.	Machine read QTcF values might be lower than central reads. Subjects are SF if the average of 3 ECGs on central read > 450 ms. Instructing sites to perform triplicate ECGs when machine reads are > 440 ms will ensure all required evaluations are completed.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.6 Table 5
Revised exclusion criterion (#19) to clarify that subjects who participated in a clinical study that involved a new chemical entity or investigational drug for Alzheimer's Disease (AD) are to be excluded	Clarification	Synopsis • Exclusion Criteria Section 9.3.2
Added events of possible abuse potential to the safety assessments for the Core Study and Extension Phase	Clarification	Synopsis • Assessments Section 9.7.1.8
Revised text to clarify that if a Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice during the Treatment Period, that is confirmed on repeat testing and within a 6-month period, then the subject should be discontinued permanently from the study drug in the Core Study.	To clarify that this applies to Treatment Period in the Core Study.	Synopsis • Assessments Section 9.3.3
Added timepoints when the NPI-10 item will be conducted in the Extension Phase	Wording added	Synopsis • Assessments
Clarified that *ApoE4* status may be included in the model if appropriate	Clarification	Synopsis • Efficacy Analyses Section 9.7.1.6.1 Section 9.7.1.6.2

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Revised Core Study analysis of biomarker endpoints to clarify that change from baseline in functional magnetic resonance imaging (fMRI) parameters as appropriate, will be determined	Clarification	Synopsis • Analysis of Biomarker Endpoints Section 9.7.1.7.3
Added that a futility analysis is planned when approximately 30% of subjects have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date	Clarification	Synopsis • Interim Analyses Section 9.7.3
Clarified that subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will need to provide separate Extension Phase-specific written informed consent	Clarification	Section 5
Added a valid period for assessment results of Tiers 1 to 5	Clarification	Section 9.1.1.1
Added information to permanent discontinuation	Clarification to cover subjects where the study drug had been temporary suspended for more than 3 weeks	Section 9.3.3
Added that termination of therapy for symptomatic treatment of AD during the study should be undertaken in compliance with local standard of care.	Clarification	Section 9.4.7
Added information on CSF sampling at Visit 13 (early discontinuation [ED])	Clarification to avoid samples being taken when subject has been off the study drug for more than 7 days.	Section 9.5.1.3.3
Revised to clarify that postdose pharmacokinetic (PK) samples will not be needed for subjects who are temporary suspended from study drug or permanently stopped the study drug at the ED visit	To clarify requirements for collection of PK samples when subjects are not being dosed.	Section 9.5.1.4.1
Added neurogranin as an	Correction	Table 2

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
Exploratory Biomarker Subset		
Added details as to when amyloid positron emission tomography (PET) and tau PET imaging will be conducted	Clarification	Section 9.5.1.4.2
Added how adverse events (AEs) will be handled for subjects who permanently discontinue study drug, but continue in the study.	Wording added	Section 9.3.3 Section 9.5.1.5.1
Added treatment changes in depigmentation/hypopigmentation/ vitiligo/loss of hair color to the list of AEs that will require the collection of information to provide detailed description of the event	AE of interest added	Section 9.5.1.5.1
Revised blood sampling for immunological assessments and added corresponding footnote	Based on Data Safety Monitoring Board recommendation	Table 5 Table 6
Revised the example of the locally approved amyloid-imaging agent to Neuraceq	To reflect main imaging agent in use during the study	Table 4 Table 5
Added a footnote to state that Visit 2 bottles of study drug will be redispensed at Visit 3	Clarification	Table 5
Added footnotes to state when initiation, termination or change in dose is permitted or that herbal medications and preparations should be discussed with the medical monitor	Clarification	Listing 4 in Section 12
Revised list of permitted medication and permitted medication if used for short-term basis	Clarification	Listing 5 in Section 12
Added footnote that herbal medications or preparations should be discussed with the medical monitor and benzodiazepines were deleted	Clarification	Listing 5 and Listing 6 in Section 12

Revisions to Version 5.0

New version/date: Version 6.0/21 Jan 2019 (per Amendment 05)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to remove "(E2609)"; grammatical, typographical, and formatting changes were also made	Correction	Throughout

Revisions to Version 4.0

New version/date: Version 5.0/19 Jul 2018 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) who have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 4 Table 5 Section 9.7.1.1.3 Section 9.7.1.7.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 5)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 4 and Table 5)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 5)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 5)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion criteria

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
		Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 5) Section 9.5.4.3.1 Section 10 Appendix 3
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis – Statistical Methods • Bioanalytical Methods Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.3 Section 9.7.1.7.3
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 4)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 5)
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analyzed.	PK analysis is no longer planned in subjects administered placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 2)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 4)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 6)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result documentation from the urine	Added for clarification	Section 11.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
dipstick test needs to be retained as source documentation.		
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted "pharmacogenomics (PGx)" data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Added new study director	To establish separate study directors in the 2 identical Phase 3 studies	PROTOCOL SIGNATURE PAGE
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4(new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSF collection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4 and Table 5) Section
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4
Revised text for amyloid CSF	Revised for clarification	Section 9.5.1.3.3

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
sampling to note that 2 methods are available rather than required		Section 9.5.1.5 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the medical monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1
Revised dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14)	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for assessments; added clarification that the volumes are estimates and may vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 6
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) $\geq$ 1.7; bilirubin $\geq$ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 4), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening.	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment.	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 4

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 3) Section 9.5.2.1 (Table 4 and Table 5)
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 3 Section 9.5.2.1, Table 5

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
by the white blood cell count × percentage of lymphocytes.		
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the Treatment Period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	Results of the special population hepatic impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	Section 7.1
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 4, and Table 5)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4, and Table 5)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"		
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 4 and Table 5)
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 5)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 6)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat (E2609)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01) V3.0 04 Apr 2017 (Amendment 02) V4.0 28 Jun 2017 (Amendment 03) V5.0 19 Jul 2018 (Amendment 04) V6.0 21 Jan 2019 (Amendment 05)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Approximately 250 global sites (revised per Amendment 05)

Study Period and Phase of Development

This Phase 3 study will consist of:

- Core Study: The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow up.
- Open-label Extension Phase: Up to 24 months of additional treatment, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first, and 1-month follow up. (revised per Amendment 05)

Core Study Objectives

Primary Objective

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD) pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 05)

Key Secondary Objectives (revised per Amendment 05)

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-302

Other Secondary Objectives (revised per Amendment 05)

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the

CDR-SB at 24 months for subjects with EAD enriched by baseline PET standardized uptake value ratio (SUVR) pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale – cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] amyloid beta [Aβ] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 05)
- To explore potential plasma and CSF biomarkers of Alzheimer's disease (AD)

(eg, neurofilament light [NFL], visinin like protein 1 [VILIP1], human cartilage glycoprotein-39 (YKL-40), and neurogranin [Ng]) (revised per Amendment 05)To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)

- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

Exploratory Objectives

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI)-10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    - EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    - Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Extension Phase Objectives (revised per Amendment 05)

Primary Objective

- To evaluate the long-term safety and tolerability of daily dosing with elenbecestat in subjects with EAD

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia, for subjects who were not clinically staged as having dementia at Core Study baseline, based on a clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is

maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by PET (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using vMRI
- To evaluate the long term-effect of elenbecestat in preserving brain connectivity as measured by task-free fMRI
- To evaluate the long-term effect of elenbecestat on CSF tau, p-tau, and Aβ levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, Ng)

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other AD pharmacotherapies
- To explore the long-term effect of elenbecestat on the NPI-10 and if available NPI-12

Study Design

The study consists of a Core Study followed by an open-label Extension Phase. The Core Study is a 24-month treatment with 3-month follow up, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list-learning task (International Shopping List Task [ISLT]). The Extension Phase is available for subjects who complete the Core Study and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 05)

Study E2609-G000-301 and Study E2609-G000-302 will be combined with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 05)

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries

7. South America

(revised per Amendment 05)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET, tau PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg, PI-2620. . (revised per Amendments 04 and 05)

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. . The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 02 and 05).

Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 04) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, ISLT, and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

For any given subject, every effort should be made to ensure that the diagnosing clinician

(responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarker analysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01 and 03) Vital signs and weight will be recorded, and a single 12-lead ECG will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities that may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task-free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both. (revised per Amendment 03) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies, respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 01 and 04)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug and is not within 3 months of a previous CSF sample). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24-month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug. (revised per Amendment 04 and 05)Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24-month

Treatment Period. (revised per Amendment 03)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 03) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 05) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter. (revised per Amendment 05)

Extension Phase

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase.

During the Extension Phase, the assessment of safety will include the recording of all AEs. In addition, vital signs, weight, safety blood and urine laboratory tests, ECGs [no central reading of ECGs], suicidality, neurological examination, NPI, and signals of abuse potential will continue to be assessed.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study) and at Visit 24/ ED, but will be abbreviated for all other timepoints.

Clinical assessments will be performed every 4 months (MMSE, FAQ) or 12 months (CDR, ADAS-cog14). Blood biomarkers and MRI will be assessed every 12 months. Optional amyloid and

tau PET and CSF biomarker assessments will be conducted at the end of 2-year open-label treatment (Extension Phase).

Subjects who complete treatment in the Extension Phase are required to complete the Follow-up Visit 1 month after the last dose.

Subjects may discontinue the open-label study drug for any reason, but will be required to complete the ED Visit (within 7 days of last dose) and the Follow-up Visit 1 month after the last dose of study drug. In addition, subjects are required to discontinue study drug if any of the criteria specified in Section 9.3.3 are met. (revised per Amendment 05)

Number of Subjects

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects; at least 850 subjects will be randomized in each study. (revised per Amendment 05)

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

Core Study

1. MCI due to AD or mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment(eg, tau:Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 03 and 05).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a

stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications that are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

Extension Phase (revised per Amendment 05)

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up Period (Visit 15) of the Core Study, and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations).
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

Core Study

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception,

which includes any of the following:

- total abstinence (if it is their preferred and usual lifestyle)
- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or

arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 03 and 05)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)
9. Results of laboratory tests conducted during Screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below LLN or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 05)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment,

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 03)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on

systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety.
    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03). If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 05)

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat
    - any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 05)
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery that requires general, spinal, or epidural anesthesia that would take place during

the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.
Study Treatments **Core Study** Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food. **Extension Phase** Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food. (revised per Amendment 05)
Duration of Treatment **Core Study:** The maximum estimated duration for each subject is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month follow-up). **Extension Phase:** The estimated duration for a subject is 25 months (ie, 24 months of treatment and 1-month follow-up. (revised per Amendment 05).
Concomitant Drug/Therapy (both Core Study and Extension Phase) The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 01) a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 01) b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 01 and 03) c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration. d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01) Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendments 02 and 05) Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendments 03 and 05)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments (both Core Study and Extension Phase)

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD. ADCOMS (Wang, et al., 2016) is a composite clinical score that represents a new approach to the analysis of selected items (12 total) from 3 fully validated and well-established clinical tools, of the MMSE, the CDR, and the ADAS-cog14. The data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412, and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change. (revised per Amendment 05)

Pharmacokinetic Assessments (Core Study Only)

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (both Core Study and Extension Phase)

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02, and 03)

Blood will be collected to measure PD and biomarkers in both the Core Study and the Extension Phase. (revised per Amendments 02, 03, and 05)

Amyloid PET imaging or CSF AD assessment (eg, tau:Aβ(1-42) ratio) or both will be used to

confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 03) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. Historical CSF samples may be analyzed to confirm amyloid pathology, if collected, processed, and stored under appropriate conditions and approved by the sponsor. (revised per Amendments 03 and 05)

Subjects who consent to participate in the amyloid and tau PET longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED visit in the Core Study and at 24 months or at the ED visit in the Extension Phase. (revised per Amendments 03, 04, and 05)

Subjects who consent to the CSF substudy will have samples taken at 24 months or at the ED visit in both the Core Study and Extension Phase for PD and biomarker assessments. (revised per Amendments 02 and 05)

Safety Assessments (both Core Study and Extension Phase)

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings (evaluated by a central reader in the Core Study); physical, dermatologic, and neurologic examinations; assessment of suicidality, events of possible signals of drug abuse potential, and MRIs during the Treatment Period. (revised per Amendments 01 and 05)

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6-month period during the Core Study treatment, then the subject should be discontinued permanently from the study drug in the Core Study. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period, then the subject should be discontinued permanently from the study drug. (revised per Amendments 01, 03, and 05).

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed

promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly until month 3 of treatment in the Core Study and until Month 2 in the Extension Phase. Thereafter, they will be monitored every 3 months in the Core Study and every 4 months in the Extension Phase until the end of the Treatment Period and at Follow-up Visits. (revised per Amendment 05)

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period in the Core Study and during the Extension Phase will require a more detailed follow-up. (revised per Amendments 03 and 05)

Other Assessments (Core Study Only)

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Other Assessments (Extension Phase Only)

The NPI-10 or if available NPI-12 will be conducted at Day 1, Month 4, Month 12, and then every 12 months. If the NPI-12 questionnaire is used, both NPI-10 and NPI-12 scores will be calculated. (revised per Amendment 05)

Bioanalytical Methods (both Core Study and Extension Phase)

CSF AD assessment (eg, tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits. (revised per Amendment 03) Exploratory biomarkers such as neurofilament NFL, Ng, YKL-40, and VILIP1 may also be measured using validated assays. (revised per Amendments 01 and 05)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 03)

Plasma concentrations of elenbecestat that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Follow-up Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 05)

Core Study

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 05)

Key Secondary Endpoints (revised per Amendment 05)

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

Other Secondary Endpoints (revised per Amendment 05)

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies

Biomarker Endpoints

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in plasma amyloid biomarker eg, Aβ(1-x) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at 24 months based on MMRM model. The LS means and

difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 05)

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 05)

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie., any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 05)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between eg, 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. *ApoE4* status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the

Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-42), t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendments 04 and 05)

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 05)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables

(in CSF, plasma) of elenbecestat as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in

ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 05)

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Extension Phase (revised per Amendment 05)

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
    - Brain amyloid and tau PET levels
    - Total hippocampal volume as measured by vMRI
    - fMRI parameters as appropriate
    - CSF t-tau, p-tau and amyloid beta (Aβ(1-42)) levels
    - Plasma and CSF amyloid beta (Aβ(1-x))
    - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
    - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

Extension Phase Analysis Sets

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase,

which include: Safety, FAS, PPS and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive an increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al, 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, the MMRM model will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET SUVR
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI
- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline in Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints. The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined

2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at the time of the futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 05)

Sample Size Rationale

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]) is selected to estimate the mean and standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group, which are 1.5 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 05)

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
ADCOMS	Alzheimer's Disease Composite Score
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval

Abbreviation	Term
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	early Alzheimer's disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

Abbreviation	Term
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata

Abbreviation	Term
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
SUVR	standardized uptake value ratio
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Council for Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 03) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 03) The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative, impartial witness, study partner). (revised per Amendment 03) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects who agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 04)

Subjects who agree to take part in the Extension Phase and the substudies during the Extension Phase, will be asked to provide separate Extension Phase-specific written informed consent. At the start of the Extension Phase, an assessment of capacity to consent should be undertaken, and continue periodically throughout the Extension Phase treatment, utilizing the method and frequency as for the Core Study above. (revised per Amendment 05)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 250 investigational sites globally. (revised per Amendment 05)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ-secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat Investigator's Brochure). Another study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat was administered orally by gavage once a day to male rats for 28 days before, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 03) Further details of the nonclinical data to date with elenbecestat can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing to assess the PK levels of elenbecestat and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open-label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat. It also investigated the effects of elenbecestat on the PK properties of digoxin. (revise per Amendment 03)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open-label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of elenbecestat under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat. (revised per Amendment 01)

Study E2609-G000-202 (Study 202) has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat given daily, along with safety and exploratory efficacy. Elenbecestat was generally well tolerated; no unexpected safety concerns emerged. Although sample sizes were small, statistically significant decreases in PET standardized uptake value ratios (SUVR) were seen. Clinical assessments suggest elenbecestat may have attenuating effects on cognitive decline in MCI-to-moderate AD subjects (Lynch, et al., 2018). Forty-three out of the 70 randomized subjects completed the study and of these 41 elected to enroll in an open-label Extension Phase. The Extension Phase has been running for 2 years and currently has 36 subjects still receiving elenbecestat. (revised per Amendment 05)

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat. In elderly subjects treated with 50 mg of elenbecestat, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects that were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or ECG parameters. The 800 mg (maximum) dose was associated with a small increase of QTc interval calculated using Fridericia's formula (QTcF) from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of

latent infections in subjects who received single doses of elenbecestat. A single dose of elenbecestat up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the Treatment Period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat when coadministered with elenbecestat but not when dosed at least 2 hours apart from elenbecestat. Elenbecestat (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat. Based on these results, it is not considered necessary to impose restrictions during elenbecestat treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications that are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when elenbecestat will not be present, as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study

confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat. The effects of elenbecestat on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50-mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat PK parameters (C_{max} and AUC). (revised per Amendments 01 and 03) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of the Core Study is:

- To determine whether elenbecestat is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302 (revised per Amendment 05)

8.2 Secondary Objectives

The key secondary objectives of the Core Study are as follows (revised per Amendment 05):

- To determine whether elenbecestat is superior to placebo on the change from baseline in Alzheimer's Disease Composite Score (ADCOMS) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD in study E2609-G000-302

The other secondary objectives of the Core Study are as follows (revised per Amendment 05):

- To evaluate the safety and tolerability of elenbecestat in subjects with EAD
- To determine whether elenbecestat is superior to placebo on the change from baseline in the CDR-SB at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the change from baseline in ADCOMS at 24 months for subjects with EAD enriched by baseline PET SUVR pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to worsening of CDR scores by 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline

based on a clinical diagnosis evaluated every 3 months pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the Alzheimer's Disease Assessment Scale – cognitive subscale14 (ADAS-cog14), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To determine whether elenbecestat is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF amyloid beta [Aβ], total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, tau PET, volumetric magnetic resonance imaging [vMRI], and functional MRI [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302
- To evaluate the population PK of elenbecestat in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat is superior to placebo on plasma amyloid levels (eg, Aβ(1-x)) at 24 months in subjects with EAD (revised per Amendment 05)
- To explore potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL), visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin (Ng) (revised per Amendment 05)
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)
- To determine whether elenbecestat is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI

- To evaluate whether elenbecestat is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of AD, as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

8.3 Exploratory Objectives

The exploratory objectives of the Core Study are:

- To explore the relationship between elenbecestat exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

For objectives specific to the Extension Phase, refer to Appendix 5 in Section 12.

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group Core Study with an open-label Extension Phase in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list-learning task (ISLT). The Extension Phase is available for subjects who complete the Core Study, including the 3-month follow up, and provides subjects with open-label treatment with elenbecestat for 24 months, or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first. (revised per Amendment 05)

Study E2609-G000-301 and Study E2609-G000-302 will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study.

In this Core Study, subjects will be randomized in a double-blind manner, to receive either placebo or elenbecestat 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region and South Africa)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

(revised per Amendment 05)

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Three longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. The tau PET substudy will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendments 04 and 05)

The maximum estimated duration for each subject in the Core Study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase, and a 3-month follow-up).

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when approximately 30% subjects in the combined 2 studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 of the Core Study. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. All subjects who enter the Extension Phase will be treated with elenbecestat, including the subjects who received placebo during the Core Study. For all subjects, assessments performed at Visit 15 will serve as baseline values for the Extension Phase. (revised per Amendment 05)

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified

to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. (revised per Amendment 05) The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

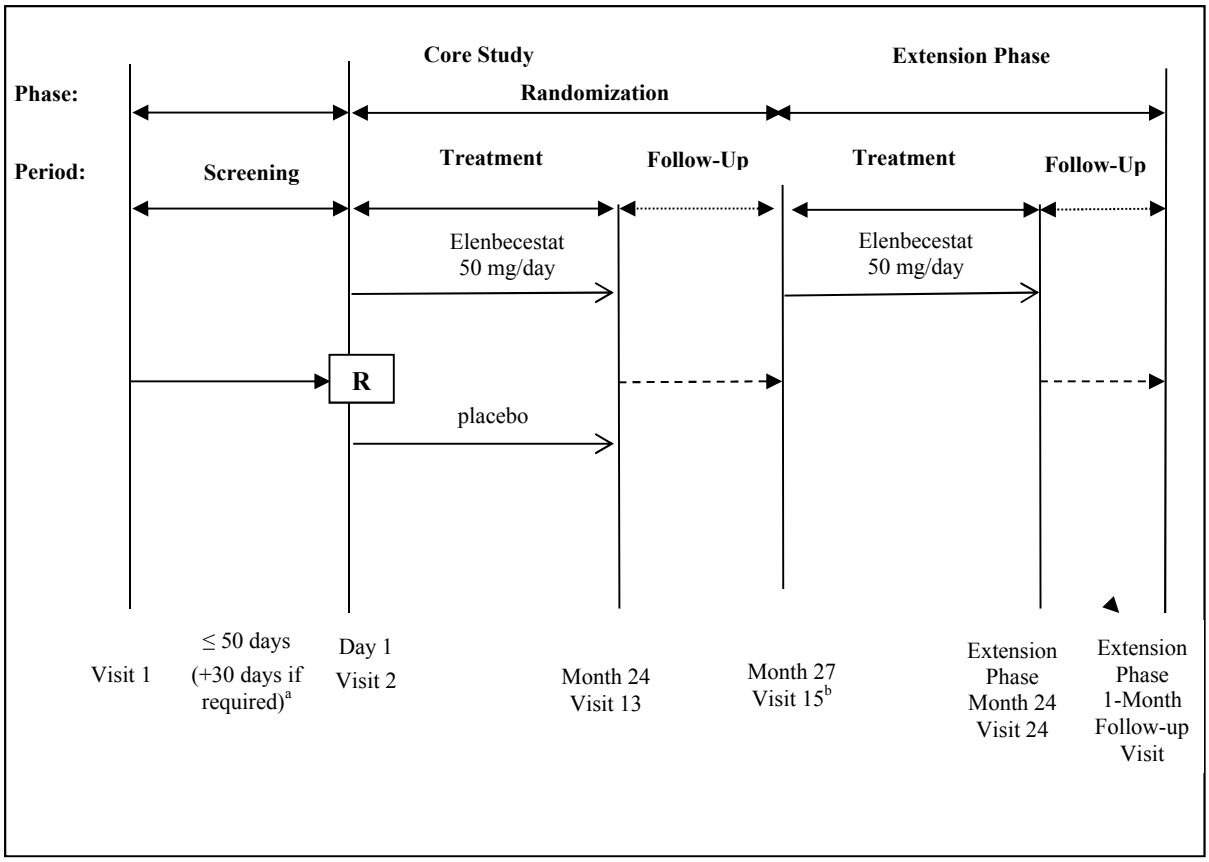

Figure 1 Study Design for E2609-G000-302 (revised per Amendment 05)

Elenbecestat = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a: Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

b: The last day of the Core Study (Visit 15) is also the first day of the Extension Phase

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained before the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5, (ie during the Randomization Phase of the study). Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 03, and 04)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of Screening. (revised per Amendment 04)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

Subjects may be re-screened, if deemed appropriate by the investigator and medical monitor. Unless otherwise stated, results of the following will be valid over the timeframes stated below: (revised per Amendment 05)

- Tiers 1 to 3 Screening will be valid for 96 days from the date of assessment
- Tier 4 MRIs will be valid for 90 days from the date of assessment
- Tier 5 CSF results and amyloid PET scans will be valid for 90 days from the date of assessment, while historical amyloid PET scans will be valid for 12 months

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, (ISLT, CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, before the CDR is administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions that may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 03)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood

samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 02 and 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 01) A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities that may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment or both. (revised per Amendment 03) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for lumbar puncture (LP) to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 03) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau

PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Screening amyloid PET and/or Screening CSF AD assessment (eg, tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. (revised per Amendment 05) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the LP. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of assessment for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 03) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment, as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 03 and 04)

During the Randomization Phase all subjects will undergo assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will have assessments at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24-month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 01, 03, and 04) CSF and PET

assessments should be conducted before any other visit assessments and while subject is still on study drug. (Refer to Table 5 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.) (revised per Amendment 05)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog14, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03) Inclusion and exclusion criteria will be reviewed again together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as needed. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 05) Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication (revised per Amendment 03). Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED Visit/Follow-up Visit. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD, and assessment of immune status are performed at different intervals throughout the Treatment Period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). CSF will be used to assess PD, PK, and exploratory biomarkers. For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. CSF and PET assessments should be conducted before any other visit assessments and while subject is still on study drug (revised per Amendments 01, 03, 04, and 05). Please refer to Schedule of Assessments (Table 5).

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the post-treatment Follow-up Period.

In some cases, UNS visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment on study drug and the 3-month follow up in the Core Study. The open-label Extension Phase will continue for 24 months, or until commercial availability of elenbecestat, or until a positive benefit-risk assessment in this indication is not demonstrated, whichever comes first (See Appendix 5 for full details of the Extension Phase) (revised per Amendments 02 and 05)

9.1.3.1 Extension Phase Follow-Up Period (revised per Amendment 05)

All subjects, regardless of whether they complete all 24 months of open-label treatment or discontinue study drug prematurely, will complete a post-treatment Follow-up Visit 1 month after the last dose of open-label study drug.

In some cases, UNS visits will be needed to follow up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments in Appendix 5) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.4 End of Study

The end of the Core Study will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. The end of the Extension Phase will be the date of the last study visit for the last subject enrolled in the Extension Phase. (revised per Amendments 02 and 05)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

Study E2609-G000-301 and Study E2609-G000-302 are multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group studies in subjects with EAD including MCI due to AD and the early stages of mild AD. The 2 studies will be combined, with a total of approximately 1900 randomized subjects; at least 850 subjects will be randomized in each study across 2 treatment groups, (placebo, 50 mg per day elenbecestat) for 24 months. (revised per Amendment 05) The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of blinded treatment in the Randomization Phase and a 3-month Follow-up Period).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured

interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog14 (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials. A novel composite endpoint, ADCOMS (Wang, et al., 2016), is also included as a secondary endpoint. (revised per Amendment 05)

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 03)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat. This is because as AD progresses

to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). Therefore, attempts to slow disease progression with elenbecestat are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog14 immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

ADCOMS is a weighted linear combination of 12 items from 3 of the above clinical scales, the ADAS-cog, the MMSE, and the CDR. These 12 items consist of the predictive variables A4, A7, A8, A11, M1, M7, C1, C2, C3, C4, C5, and C6. The names of these items and the corresponding scale names are described in Table 1. Data from 4 studies, including the Alzheimer's Disease Neuroimaging Initiative (ADNI), ADCS-008, E2020-A001-412 and E2020-E033-415 have been used in a statistically validated model aimed at optimizing sensitivity to disease progression over time in the MCI population, allowing earlier detection of clinical change.

Table 1 Predictive Variables for the ADCOMS

Scale	Item ID	Item Name	PLS weight
ADAS-cog	A4	Delayed Word Recall	0.00847483
	A7	Orientation	0.017088
	A8	Word Recognition	0.003732761
	A11	Word Finding	0.016211
MMSE	M1	Orientation Time	0.041567
	M7	Drawing	0.038238
CDR	C1	Personal Care	0.054321
	C2	Community Affairs	0.1091
	C3	Home and Hobbies	0.089039
	C4	Judgment and Problem Solving	0.069493
	C5	Memory	0.058724
	C6	Orientation	0.078152

ADAS-cog = Alzheimer's Disease Assessment Scale, cognitive subscale, CDR = Clinical Dementia Rating, ID = identification, MMSE = Mini Mental State Examination, PLS = Partial Least Squares.

(revised per Amendment 05)

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat treatment.

9.2.4 Rationale for Biomarkers

CSF biomarkers, amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a LP procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 04)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ[1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 03)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 03) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 04)

Tau PET imaging will be performed to evaluate the effects of elenbecestat on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later

stages. For this reason, hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as NFL, Ng, VILIP1, or YKL-40) become available. (revised per Amendments 01, 02, and 05)

9.3 Selection of Study Population

At least 850 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 250 centers worldwide. (revised per Amendment 05) Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

Core Study

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.

4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, tau: Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor. Historical CSF samples, if collected, processed, and stored under appropriate conditions and approved by the sponsor, may be analyzed to determine CSF amyloid positivity. (revised per Amendments 03 and 05).
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks before Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks before Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

For inclusion criteria specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendments 03 and 05).

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during Screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendment 01)

- Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

- Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN). Levels of Vitamin B12 may be confirmed with reflex testing to include methylmalonic acid (MMA) analysis, if available in region. (revised per Amendment 05)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy

      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the medical monitor. (revised per Amendment 03)

    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTcF interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. (revised per Amendment 05)

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months before Screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

- any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat

- any new chemical entity or investigational drug for AD with last study drug dose occurring within 6 months before Screening unless it can be documented that the subject received only placebo (revised per Amendment 05)

- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery that requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Absolute lymphocyte count will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the ALC test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than 800/mm^3. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of ALC will follow the schedule of assessments (Table 5) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs twice within a 6 month period, during the Core Study Treatment Period, then the subject should be discontinued permanently from the study drug. In the Extension Phase, if a confirmed Grade 2 or greater lymphocytopenia (less than 800/mm^3) occurs twice from Visit 16 onwards during a 6-month period then the subject should also be discontinued permanently from study drug (revised per Amendments 01, 03, and 05).

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 01 and 02) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥1.7; bilirubin ≥1.5×ULN; albumin <LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 02)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 02)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-up Visits (1 and 3 months after the last dose of study

drug). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

For subjects who temporarily suspend study drug (eg, ALC <800/mm^3) but progress to permanently discontinue study drug, the ED and Follow-up Visits should be scheduled as follows: (revised per Amendment 05)

- If ≥ 3 weeks since the last study dose, then the ED Visit should be scheduled immediately, and the 1-month Follow-up Visit will not be required
- If <3 weeks since the last study dose, then the ED visit should be scheduled immediately, and Follow-up Visits at 1 and 3 months after the last dose will be required

All subjects in the Core Study who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications.. New AEs will be collected for 4 weeks post last dose and followed up for 12 weeks, or until resolution, whichever comes first. AEs relating to study procedures will be collected until the end of study participation. (revised per Amendment 05) However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug eCRF page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

Core Study For this study, the test drug is elenbecestat and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 5 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the Treatment Period, the investigator should discuss with the medical monitor whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

For details on treatment to be administered in the Extension Phase, refer to Appendix 5 in Section 12.

9.4.2 Identity of Investigational Product(s)

Core Study

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat

- Test drug code: E2609
- Generic name: elenbecestat
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 has been completed, and a study report is in preparation. It evaluated the PD effects (reduction from baseline in CSF Aβ levels) along with safety and exploratory efficacy of 5, 15, and 50 mg of elenbecestat given daily. Based on the PK/PD modeling results,

elenbecestat 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 02) Based on these data, elenbecestat 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject before the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the Treatment Period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the Treatment Period (revised per Amendment 01)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the Treatment Period (revised per Amendments 01 and 03)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation or termination of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD (revised per Amendment 02 and 05). Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the medical monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including opiates and short-term use of benzodiazepines) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours before cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication before CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug that is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable

- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 Medical History and Physical Examinations

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 4 and Table 5. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog14 are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 Psychometric Assessments

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a

clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment, and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog14: The ADAS-cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-cog14 that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-cog14. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0 to 10. (revised per Amendment 02)

ADCOMS: ADCOMS is a composite score of 12 items from the CDR, MMSE, and ADAS-cog, and does not require any additional assessments. (revised per Amendment 05)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 4 and Table 5, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task-free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7 to 10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available at screening to determine subject eligibility for the study. (revised per Amendment 02) Subjects who undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal.

CSF samples at Visit 13 should be collected while the subject is still on the study drug and before the other visit assessments. All ED CSF samples need to be taken no later than 7 days

after the last dose of study drug. All CSF samples should be taken at approximately the same time of day as at the Screening Visit. (revised per Amendment 05)

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to the CSF procedure at Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat. Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 03) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 4 and Table 5. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporary suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose PK samples are not required. (revised per Amendment 05)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 2 lists PD, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 03)

Table 2 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments (revised per Amendment 05)

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Example of Exploratory Biomarkers	PD	Example of Exploratory Biomarkers
Whole Blood/ Plasma	ApoE [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) Aβ42/Aβ40 ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 Tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers	PD	CSF AD Biomarkers	Example of Exploratory Biomarkers
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1 Neurogranin

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)

a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 02 and 03)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 02 and 03)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 4 and Table 5. (revised per Amendment 02) The blood sample collected for PD analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 03)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the

event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 02 and 03) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 03) The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

For subjects participating in the amyloid PET substudy, amyloid PET imaging will be conducted on separate days from the scheduled visits and should be conducted before the clinic Visit 9 and no later than 7 days after the last dose for Visit 13/ED. (revised per Amendment 05)

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 04)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED Visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED Visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

For subjects participating in the tau PET substudy, tau PET imaging will be conducted on separate days from the scheduled visits and should be conducted before clinic Visit 13/ED and no later than 7 days after the last dose of study drug. (revised per Amendment 05)

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities that will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 04)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 4 and Table 5); and MRIs as detailed in Table 4 and Table 5. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 4 and Table 5. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs that will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the Core Study. (revised per Amendment 05)

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF until 4 weeks post last dose, and followed up for 12 weeks, or until resolution, whichever comes first (as shown in Table 5). Adverse events relating to study procedures will be collected until the end of study participation. Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. (revised per Amendment 05)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog14, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form during the Treatment Period and first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). (revised per Amendment 03).

Euphoria-related terms: (revised per Amendment 03)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 03)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 03)

- Somnolence (revised per Amendment 03)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 03)

- Psychosis

- Aggression (revised per Amendment 03)
- Confusion and disorientation (revised per Amendment 03)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 03)

- Drug tolerance
- Habituation (revised per Amendment 03)
- Substance related disorders (revised per Amendment 03)

Physical dependence or withdraw (only for events observed within 14 days of the last dose of study drug): (revised per Amendment 03)

- Drug withdrawal syndrome (revised per Amendment 03)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following AEs will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the medical monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); treatment-emergent depigmentation/ hypopigmentation/vitiligo/loss of hair color; amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality (revised per Amendments 02 and 05).

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.

(revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild Discomfort noticed, but no disruption of normal daily activity

Moderate Discomfort sufficient to reduce or affect normal daily activity

Severe Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug

- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. Table 4 and Table 5 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), prothrombin time, INR (derived from prothrombin time) and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 01 and 02). A prothrombin time and INR should also be performed before LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 (with reflex MMA if available for low vitamin B12) (revised per Amendment 05) Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing if required. (revised per Amendments 02 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

Table 3 Clinical Laboratory Tests

Category	Parameters

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, MMA = methylmalonic acid, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 4 and Table 5 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 Physical Examinations

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 5. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 4 and Table 5. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition, subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 02) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the medical monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 5 and will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS

pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 4 and Table 5. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF machine read is greater than 440 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader. (revised per Amendment 05).

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 4 and Table 5. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments. If subjects have non-MRI compatible devices fitted during treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator. (revised per Amendment 05)

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 5).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 4 and Table 5, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?" (revised per Amendment 02) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered (revised per Amendment 02). A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the medical monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at Screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 5 presents the schedule of procedures/assessments for the Randomization Phase.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendment 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendment 02)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 02)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 04)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 03 and 04)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QTcF = QTc interval calculated using Fridericia's formula, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study). (revised per Amendment 04)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, before the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR derived from the prothrombin time, and aPTT are to be performed as part of Screening (revised per Amendments 01 and 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 03) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 02)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Neuraceq, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 90 days from the date of the original screening procedure. (revised per Amendments 04 and 05)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 2 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendments 04 and 05).

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Consent (subject and study partner)															X[dd]	
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X														X[dd]	
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (revised per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, (revised per Amendment 02) [ee]	X	X	X	X	X	X	X	X								
PBMCs for storage and testing required (revised per Amendment 05)	X					X		X				X	X			
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X	X[dd]	X

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog14[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI-10	X					X		X		X		X	X		X[hh]	
C-SSRS	X	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X[gg]	X	X		X[dd]	
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X[ii]	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X		X[cc]	
Tau PET (optional substudy) [u]												X	X		X[cc]	

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[y]												X	X		X[cc]	
Adverse events[ff]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[bb]	X	X	X	X	X	X	X	X	X	X				X[dd]	

Notes

ADAS-cog14 = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, QTcF = QTc interval calculated using Fridericia's formula, UNS = unscheduled, vMRI = volumetric MRI.

a: A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visits 7 to 13 inclusive (including for subjects who discontinue study drug early but who return for clinical assessments at 12 and 24 months). These windows should be calculated from Day 1. A window of ±3 days calculated from the last dose will be permitted for the Follow-up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

b: Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog14) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications. New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-up Visits (Visit 14 and Visit 15).

c: All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm3) during the Follow-up Period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. Visit 15 will also act as Baseline for subjects who successfully complete the Core Study and will be enrolled into the open-label Extension Phase. (revised per Amendments 01 and 05)

d: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e: Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15 or if the subject is continuing in the Extension Phase.

f: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

g: A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED) and Visit 15 if entering the Extension Phase (revised per Amendment 05). Neurologic examinations at the other visits will focus on new symptoms and signs that will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h: Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i: Single 12-lead standard ECGs will be recorded. If the QTcF machine read is greater than 440 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values. (revised per Amendment 05)

j: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k: More frequent testing may be required per local regulations. (revised per Amendment 03) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l: Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m: Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
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Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 03)

n: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

o: Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

p: The clinical assessment of suicidality will require input from both the subject and the study partner

q: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

r: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

s: MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the medical monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t: Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuraceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 03 and 04)

u: For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 04)

v: Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w: Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED), the trough PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If the study drug is temporarily suspended, postdose PK samples will not be required. If at an ED Visit, the subject has already stopped study drug, postdose

Table 5 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendments 04 and 05)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

PK samples are not required.

x: PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 02 and 03)

y: For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

z: Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

aa: AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 01 and 03)

bb: The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03) Visit 2 bottles are re-dispensed at Visit 3 after accountability is performed. (revised per Amendment 05)

cc: Only for Extension Phase subjects who did not participate in optional longitudinal substudies in the Core Study but who wish to consent to optional longitudinal substudies in the Extension Phase.

dd: For subjects entering the Extension Phase only.

ee: Immunological assessments only required for subjects randomized before 07 Sep 2018ff: New AEs will be collected for 4 weeks post last dose and followed-up for 12 weeks, or until resolution, whichever comes first. If >4 weeks post last dose, AEs relating to study procedures will be collected only

gg: C-SSRS to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior

hh: For those subjects entering the Extension Phase, NPI-12 will be used if available and both NPI-10 and NPI-12 scores calculated.

ii: Not required for those entering Extension Phase

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 4 and Table 5 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 4). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 6 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 02) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 02)

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 02 and 03)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 03)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 02 and 03)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 02)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 02 and 03)	1	none	1×3.5 mL	none	3.5 mL

Table 6 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening and MMA where available (revised per Amendments 02, 03, and 05)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, (revised per Amendments 03 and 05)[b]	8		1×10 mL	7×10 mL	80 mL
Blood for PBMCs (revised per Amendment 05)	4	none	1×10 mL	3×10 mL	40 mL
Blood for immune status (revised per Amendment 03)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 01, 02, and 03)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendment 02)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendments 01 and 02)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 01, 02, 03, and 05)		25.8 mL	46.8 mL	298.9 mL	371.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Follow-up Visit) ; actual volume may vary based on local regulations. (revised per Amendment 02)
b: Immunological assessment samples not required for subjects randomized after 07 Sep 2018 - reducing total blood volume to 291.5 mL (revised per Amendment 05)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 4 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion. (revised per Amendment 05)

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 03)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 03)

9.5.4.3.2 REPORTING OF STUDY-SPECIFIC EVENTS

Study-specific events (ocular herpes, new onset seizures, and symptomatic cerebral vasogenic edema), as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 5 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24-month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedures, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

For statistical methods specific to the Extension Phase, refer to Appendix 5 in Section 12.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding. All statistical analyses will be performed based on the pooled data from 2 studies (E2609-G000-301 and E2609-G000-302). The analyses will also be performed within each study to confirm the trend of the efficacy and biomarker endpoints unless specified. (revised per Amendment 05)

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months in the combined studies (revised per Amendment 05)

9.7.1.1.2 SECONDARY ENDPOINTS

The key secondary endpoints of the study are as follows (revised per Amendment 05):

- Change from baseline in ADCOMS at 24 months in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
- Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

The other secondary endpoints of the study are as follows (revised per Amendment 05):

- Change from baseline in the CDR-SB at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- Change from baseline in the ADCOMS at 24 months for subjects enriched by baseline PET SUVR, eg, between 1.2 and 1.6, in the combined studies
- The rate of change over time (mean slope) based on CDR-SB score over 24 months in the combined studies
- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken) in the combined studies

- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis in the combined studies
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in the combined studies
- Change from baseline in ADAS-cog14, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in the combined studies

9.7.1.1.3 BIOMARKER ENDPOINTS

The biomarker endpoints of the study are:

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.1.4 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.

- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog14, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include fixed effects of treatment group, visit, treatment group by visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, and randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization [Visit 2] [yes, no]). *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat versus placebo will be compared at

24 months based on MMRM model. The LS means and difference in LS means between elenbecestat treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors. *ApoE4* status may be included in the model if appropriate. Additional sensitivity analyses will be performed to assess the robustness of the missing at randomization assumption in the primary MMRM model.

Subgroup analysis (eg, stratification factors and *ApoE4* status) and additional sensitivity analysis for the primary endpoint will be performed as appropriate. (revised per Amendment 05)

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

Analyses for Key Secondary Efficacy Endpoints (revised per Amendment 05):

The key secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat 50 mg/day versus placebo, for each key secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant.

The change from baseline in ADCOMS at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline ADCOMS in the model.

The change from baseline in amyloid PET SUVR at 24 months will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline amyloid PET SUVR in the model. The same analysis will be performed within study as key secondary efficacy endpoint analyses.

Analyses for Other Secondary Endpoints (revised per Amendment 05)

The change from baseline in CDR-SB and ADCOMS at 24 months will be analyzed using the same MMRM model as the primary analysis for subjects enriched by baseline PET SUVR between e.g. 1.2 and 1.6 on the FAS.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include treatment group, baseline CDR-SB, randomization stratification variables, assessment time, baseline CDR-SB-by-assessment time, and treatment group-by-assessment time. ApoE4 status may be included in the model if appropriate.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of the Treatment Period of the Core Study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05) Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-x), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 03, 04, and 05) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, with treatment group and randomization stratification variables, as factors. *ApoE4* status may be included in the model if appropriate. (revised per Amendment 05)

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat. The effect of covariates (ie, demographics) on elenbecestat PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically and any emergent relationship

will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change from Baseline for 24 months in ADAS-cog14, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in fMRI parameters as appropriate (revised per Amendment 05)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments (revised per Amendment 05)
- Change from baseline in potential plasma and CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng) (revised per Amendment 05)

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, events of possible signals of drug abuse potential, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group. (revised per Amendment 05)

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 03)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the Treatment Period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog14, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated for comparison of elenbecestat versus placebo with respect to a pooled analysis of studies E2609-G000-301 and E2609-G000-302 for the change from baseline in CDR-SB at 24 months. Based on the available data from the placebo group in Study BAN2401-G000-201 (a recently completed study with a comparable subject population), the mean and the standard deviation of the change from baseline in CDR-SB at 24 months in the placebo group are assumed to be 1.46 and 2.05, respectively, instead of 1.75 and 2.05, which are originally assumed by the available data from ADNI (of amyloid positive, MMSE equal or greater than 24, late MCI [global CDR=0.5, CDR memory box≥0.5]). Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for elenbecestat compared to placebo with common standard deviation of 2.05 and 30% dropout rate, a total sample size of 1900 subjects, 950 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat and placebo using a 2-sample t test with 90% power at a significance level of 2 sided alpha =0.05.

The pooled data from 2 studies (E2609-G000-301 and E2609-G000-302) will comprise the total sample size of approximately 1900 subjects. At least 850 subjects will be randomized in each study. (revised per Amendment 05)

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when approximately 30% subjects in the combined two studies (E2609-G000-301 and E2609-G000-302) have had an opportunity to complete the 24-month visit of the Core Study by the interim cutoff date. The sponsor

may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data before the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study before completion of enrollment. The standard deviation of the primary endpoint was originally estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observational study. (revised per Amendment 05)

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data, which includes measures of cognitive safety at the group level, up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter. (revised per Amendment 05)

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation))
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<$3.0 – 2.0\times10^9$/L <3000 – 2000/mm^3	<$2.0 – 1.0\times10^9$/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <$0.8 – 0.5\times10^9$/L	<500 – 200/mm^3 <$0.5 – 0.2\times10^9$/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<$1.5 – 1.0\times10^9$/L <1500 – 1000/mm^3	<$1.0 – 0.5\times10^9$/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<$75.0 – 50.0\times10^9$/L <75,000 – 50,000/mm^3	<$50.0 – 25.0\times10^9$/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 01 and 03)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 03)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Initiation, termination or change in dose is permitted if in line with local standard of care. Any changes are required to be stable for 4 weeks before any cognitive assessments.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of cognitive enhancements then they should follow the same rules as the medications in this listing. (revised per Amendment 05)

Listing 5 Medications Permitted if Used on PRN or Short Term Basis (2 to 4 Weeks) Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Benzodiazepines (revised per Amendments 03 and 05)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Sedatives	
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	

PRN = Pro re nata

This list is not exhaustive.

Herbal medications or preparations should be discussed with the medical monitor. However, if they have claims of negative effects on cognition, they should follow the same rules as the medications in this listing. (revised per Amendment 05)

Listing 6 Permitted Medications

If to be used on a PRN basis, see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 03)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 03)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts

Categories (revised per Amendment 03)			**Examples**[a]	
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 03)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 03)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere	**16**	**Drug tolerance**	Drug tolerance	

Categories (revised per Amendment 03)			**Examples**[a]	
(revised per Amendment 03)	**17**	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 03)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 03)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 03)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetic (PK) or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report that can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 03)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 03) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

Appendix 5 Open-label Extension Phase (revised per Amendment 05)

Primary Objective

- To assess the long-term safety and tolerability of daily dosing with elenbecestat in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the long-term effects of elenbecestat on Clinical Dementia Rating –Sum Of Boxes (CDR-SB), Alzheimer's Disease Composite Score (ADCOMS), Mini Mental State Examination (MMSE), Functional Assessment Questionnaire (FAQ), Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog14), and ADAS-cog14 Word List (immediate recall and delayed recall)
- To evaluate the time to conversion to dementia for subjects who were not clinically staged as having dementia at Core Study baseline, based on clinical diagnosis
- To evaluate whether the treatment benefit of elenbecestat at the end of the Core Study is maintained over time in the Extension Phase

Biomarker Objectives

- To evaluate the long-term effect of elenbecestat on brain amyloid and tau levels as measured by positron emission tomography (PET) (optional substudy)
- To evaluate the long-term effect of elenbecestat on hippocampal atrophy as measured by changes in hippocampal volume using volumetric magnetic resonance imaging (vMRI)
- To evaluate the long-term effect of elenbecestat in preserving brain connectivity as measured by task-free functional magnetic resonance imaging (fMRI)
- To evaluate the long-term effect of elenbecestat on CSF t-tau, p-tau, and amyloid beta (Aβ) levels (optional substudy)
- To evaluate the long-term effect of elenbecestat on plasma amyloid (eg, Aβ(1-x)) levels
- To explore the long-term effect of elenbecestat on potential plasma and CSF biomarkers of AD (eg, neurofilament (NFL),visinin like protein 1 (VILIP1), human cartilage glycoprotein-39 (YKL-40), and neuroganin [Ng])

Exploratory Objectives

- To explore the long-term effect of elenbecestat on the initiation or dose increase of other Alzheimer's disease (AD) pharmacotherapies
- To explore the long-term effect of elenbecestat on the Neuropsychiatric Inventory (NPI)-10 and if available NPI-12

Eligibility Criteria

Subjects who do not meet all of the inclusion criteria will not be eligible to receive study drug.

Inclusion:

1. Subjects who complete the 24-month Treatment Period and the 3-month Follow-up period (Visit 15) of the Core Study and whose Visit 15 falls within a 4-week window from the start of the Extension Phase. Subjects who discontinue study drug early are not considered to have 'completed' the Core Study.
2. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations)
3. Subjects must continue to have an identified study partner who is willing and able to provide follow-up information on the subject throughout the course of the Extension Phase.

Study Design and Plan

The Extension Phase allows eligible subjects to receive elenbecestat 50 mg for up to 24 months (2 years), or until commercial availability of elenbecestat or a lack of positive benefit-risk is determined, whichever comes first.

Subjects who are enrolled and complete the Core Study, including the 3-month follow-up period, will have the option to participate in the Extension Phase. Subjects who discontinue from study drug during the Core Study are not eligible to participate in the Extension Phase.

Eligible subjects may enter the Extension Phase immediately following the completion of Core Study Visit 15. Subjects who are eligible to participate in the Extension Phase but who do not transition to the Extension Phase on the day of Visit 15 may enter the Extension Phase any time within 4 weeks of Visit 15. For all subjects, assessments performed at Visit 15 may serve as baseline values for the Extension Phase.

Subjects may discontinue from the open-label study drug for any reason but are required to complete the Early Discontinuation (ED) Visit (within 7 days of last dose). In addition, subjects are required to discontinue the open-label study drug if any of the criteria specified in Section 9.3.3 (Removal of Subjects from Therapy or Assessment) are met.

Subjects who complete the Extension Phase treatment, or discontinue the study drug are required to complete the Follow-up Visit, 1 month after their last dose. The study will end when the last subject has completed the last Extension Phase study visit.

Treatment

Elenbecestat will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets. Each subject will receive 1 tablet of 50 mg elenbecestat, to be administered orally QD in the morning with or without food.

Assessments

Assessments will be conducted as shown in Table 5 Visit 15 (Day 1 of the Extension Phase) and as shown in Table 9 for all other Extension Phase visits following the guidelines as indicated for the Core Study in Section 9.5. Concomitant therapy is allowed as stated in Section 9.4.7 and treatment compliance and accountability will be performed as indicated in Section 9.4.8 and Section 9.4.9, respectively.

Safety assessments (physical examinations, neurological examinations, vital signs, safety laboratory tests, ECGs [no central reading of ECGs], signals of potential abuse, pregnancy test for females of child-bearing potential, Columbia Suicide Severity Rating Scale (C-SSRS), and assessment of suicidal thinking/behavior, immunological assessments, safety magnetic resonance imaging (MRI) will be monitored according to Table 9 and all adverse events (AEs) and serious adverse events (SAEs) recorded.

A full neurologic examination will be performed at the start of the Extension Phase (during Visit 15, the last visit of the Core Study), and Visit 24/ED, but will be abbreviated for all other timepoints.

Safety laboratory blood tests will be collected as indicated in Table 9 and analyzed by a central laboratory.

Blood samples for pharmacodynamic (PD) and biomarker analyses (Table 7) will be collected as indicated in Table 9. The blood sample for PD analyses should be collected at fasting or at least 2 hours after the most recent meal.

Subjects that have consented to the optional CSF substudy (either at the start of the Core Study or Extension Phase) will have samples taken as indicated in the Table of Assessments to analyze PD and biomarkers (Table 7). Longitudinal CSF sample is taken before other Visit 24 assessments and whilst subject is still on study drug; for ED, CSF should be taken no longer than 7 days after the last dose.

Safety brain MRI, vMRI, and fMRI assessments will be performed at the end of the Extension Phase Treatment Period (Visit 24 or ED). Additional safety MRI scans are to be performed as clinically necessary. MRI acquisition and interpretation will be conducted centrally. If subjects have non-MRI compatible devices fitted during Extension Phase treatment, then a computed tomography scan may be utilized to assess safety, if deemed appropriate by the investigator.

Table 7 Extension Phase Samples

Sample	PD	AD Biomarkers	Example of Exploratory Biomarkers
Blood	Aβ(1-x)		Tau NFL VILIP1 YKL-40
CSF		Aβ(1-42) Tau p-tau	NFL Neurogranin VILIP1 YKL-40

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg, 1-42]), CSF = cerebrospinal fluid, NFL = neurofilament light, VILIP1 = visinin like protein 1, YKL 40 = human cartilage glycoprotein-39

Optional amyloid and tau PET assessments will be performed at the end of the Extension Phase Treatment Period before other Visit 24/ED assessments and when subjects are still on the study drug and no more than 7 days after the last dose of study drug. Subjects may consent to participate in the PET substudies at the start of the Extension Phase, for whom an additional assessment will be conducted at Visit 15 (before the first dose of the open-label study drug). PET scan acquisition and interpretation will be conducted centrally.

Assessment of suicidal ideation and behavior using the C-SSRS will be performed at the start of the Extension Phase and at the end of treatment and a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive answer to any clinical assessment of suicidality question (subject or study partner) requires the C-SSRS to be performed; any positive finding on the C-SSRS requires a psychiatric evaluation to be conducted.

Clinical assessments (MMSE, FAQ, CDR, ADAS-cog14, disease staging, NPI) will be administered as described in the Schedule of Assessments (Table 9) and a central review employed to ensure global standardization. If available the NPI version 12 (NPI-12) questionnaire will be used, but both NPI-10 and NPI-12 scores will be calculated.

The Follow-up Visit will take place at 1 month after the last dose of study drug as described in Table 9. These assessments will also be performed if a subject prematurely discontinues from the Extension Phase.

The number of blood samples and the total volume of blood that will be collected throughout the Extension Phase, are summarized in Table 8.

Table 8 Summary of Sample Volumes

Assessment	Total number of collection time points[a]	Number of time points x volume per collection (mL)	Total volume (mL)
		Extension Phase Treatment and Follow-up Periods	
Blood			
Safety labs	11	11×6.3 mL	69.3 mL
PD & biomarker sample	3	3×6 mL	18 mL
Total volume blood collected			**87.3 mL**
CSF PD and biomarker	2[a]	2×12mL	24 mL

CSF = cerebrospinal fluid, PD = pharmacodynamic
a: For subjects who consented to the CSF substudy in the Core Study, only 1 sample (12ml) is required to be collected

EXTENSION PHASE STATISTICAL METHODS

Primary Endpoint

- Safety endpoints: AE, vital sign, ECG, physical examination, neurological examination, laboratory safety test, suicidality assessment, events of possible signals of drug abuse potential, and MRI safety parameters

Secondary Endpoints

- Changes from Core Study baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia on clinical diagnosis at Core Study baseline, based on clinical diagnosis

Biomarker Endpoints

- Changes from Core Study baseline in:
  - Brain amyloid and tau PET levels
  - Total hippocampal volume as measured by vMRI
  - fMRI parameters as appropriate
  - CSF t-tau, p-tau and amyloid beta (Aβ(1-42) levels
  - Plasma and CSF amyloid beta (Aβ(1-x))
  - CSF biomarkers of AD (eg, NFL, VILIP1, YKL-40, and Ng)
  - Blood biomarkers of AD (eg, NFL, VILIP1, YKL-40)

Exploratory Endpoints

- Changes from Core Study baseline in NPI-10 and if available NPI-12

- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

EXTENSION PHASE ANALYSIS SETS

The analysis sets defined in the Core Study will also be used for the analyses in the Extension Phase, which include: Safety, Full Analysis Set (FAS), Per Protocol Analysis Set (PPS), and PD Analysis Set.

Safety Analyses

Safety analysis will be performed similarly to analyses in the Core Study. The Core Study baseline will be used for subjects who are randomized to elenbecestat initially, the Extension Phase baseline will be used for subjects who are randomized to placebo but receive elenbecestat during the Extension Phase. The incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), out-of-normal-range laboratory safety test variables, abnormal ECG findings, out-of-range vital signs, suicidality (C-SSRS), and changes from baseline in laboratory safety test variables, ECGs, safety MRI, vital sign measurements will be summarized by using descriptive statistics.

Efficacy Analyses

The following efficacy endpoints will be summarized by descriptive statistics and graphs:

- Changes from baseline in CDR-SB, ADCOMS, MMSE, FAQ, ADAS-cog14, and ADAS-cog14 Word List (immediate recall and delayed recall)
- Time to conversion to dementia for subjects who were not clinically staged as dementia based on clinical diagnosis at Core Study baseline based on clinical diagnosis
- Change from baseline in NPI-10 and NPI-12
- Proportion of subjects who receive increase and/or initiation of other AD pharmacotherapies

A delayed-start analysis (Liu-Seifert et al, 2015) will be performed for each efficacy endpoint at various scheduled visits in the Extension Phase. In addition, a mixed effects model for repeated measures (MMRM) will be used to analyze the above endpoints where appropriate.

Biomarker Analyses

The following biomarker endpoints will be summarized by descriptive statistics and graphs:

- Change from baseline in amyloid PET standardized uptake value ratio (SUVR)
- Change from baseline in tau PET signal
- Change from baseline in total hippocampal volume as measured by vMRI
- Change from baseline in the preservation of connectivity as measured by fMRI

- Change from baseline in t-tau, p-tau, Aβ(1-42) and Aβ(1-x) in CSF
- Change from baseline Aβ(1-x) in plasma
- Change from baseline in exploratory biomarkers eg, NFL, VILIP1, YKL-40, and Ng in CSF and plasma

A delayed-start analysis and MMRM model will be used to analyze these biomarker endpoints.

The relationship between efficacy endpoints and biomarker endpoints will be explored using correlation analysis.

Sample Size Rationale

Not applicable.

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since first dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs, including respiratory rate[d]	X	X	X	X	X	X	X	X	X	X	X	X
Blood samples for clinical chemistry, hematology, and coagulation	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[g]	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events[l]	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[h]	X	X	X	X	X	X	X	X	X	X	X	X
MMSE[i]				X	X	X	X	X	X	X		
FAQ[i]				X	X	X	X	X	X	X		
Disease staging						X			X	X		
12-lead ECG[f]		X		X		X			X	X	X	X
NPI[o]				X		X			X	X		
CDR[i]						X			X	X		
ADAS-cog14[j]						X			X	X		
Neurological examination[e]						X			X	X	X	X
Weight						X			X	X		X
Blood sample for PD & biomarkers[j]						X			X	X		
MRI (safety, volumetric and functional sequences)						X			X	X		
Tau PET (optional substudy)									X	X		
Amyloid PET (optional substudy)									X	X		

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	**Extension**											
Period	**Treatment[a]**										**1 Month Follow-Up**	**UNS[c]**
Day in Extension Phase	**15**	**29**	**57**	**120**	**245**	**365**	**484**	**610**	**729**	**ED[b]**		
Visit	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**			
Weeks elapsed since 1st dose in Extension Phase	**2**	**4**	**8**	**17**	**35**	**52**	**69**	**87**	**104**			
Nominal months elapsed since first dose in Extension Phase	**0.5**	**1**	**2**	**4**	**8**	**12**	**16**	**20**	**24**			
Procedures/Assessments												
CSF sampling for PD & biomarkers (optional substudy)[k]									X	X		
C-SSRS	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X[n]	X	X		
Clinical assessment of suicidal thinking and behavior	X	X	X	X	X	X	X	X			X	X
Dispense study drug	X[m]	X	X	X	X	X	X	X				

ADAS-cog = Alzheimer's Disease Assessment Scale - cognitive subscale, AE = adverse event, CBP = child-bearing potential, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, FAQ = Functional Assessment Questionnaire, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PD = pharmacodynamic, PET = positron emission tomography, QTcF = QTc interval calculated using Fridericia's formula, UNS = Unscheduled Visit

a: A window of ±3 days will be permitted for Visits 16 and 17. A window of ±7 days will be permitted for Visits 18 and 19. A window of ±10 days will be permitted for Visit 20 to 24 inclusive. These windows should be calculated from Extension Phase Day 1. A window of ±3 days will be permitted for the Follow-up Visit calculated from the last Extension Phase dose.

b: Subjects who permanently discontinue taking study drug before end of treatment will undergo an ED Visit within 7 days of their last dose of study drug. In addition, a Follow-up Visit will be scheduled 4 weeks after the last dose of study drug.

c: Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator.

d: Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

e: A full neurologic examination will be performed at Visit 24 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs.

f: Single 12-lead standard ECGs will be recorded. If the QTc interval calculated using Fridericia's formula (QTcF) machine read is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

g: If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis

h: More frequent testing may be required per local regulations. If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

i: The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws).

j: PD and biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose.

k: For subjects who consent to participate in the CSF longitudinal substudy. Visit 24 (or ED) also includes blood PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by lumbar puncture (LP) between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 39 weeks of treatment or 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects

Table 9 Schedule of Procedures/Assessments in Extension Phase

Phase	Extension											
Period	Treatment[a]									ED[b]	1 Month Follow-Up	UNS[c]
Day in Extension Phase	15	29	57	120	245	365	484	610	729			
Visit	16	17	18	19	20	21	22	23	24			
Weeks elapsed since 1st dose in Extension Phase	2	4	8	17	35	52	69	87	104			
Nominal months elapsed since first dose in Extension Phase	0.5	1	2	4	8	12	16	20	24			
Procedures/Assessments												

receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and International Normalized Ratio (INR) (derived from prothrombin time) before LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures.

l: New AEs to be collected 4 weeks post last dose, and followed-up until resolution, or until 12 weeks post last dose, whichever comes first. If >4 weeks post last dose only AEs relating to study procedures will be collected.

m: Visit 15 bottles are re-dispensed at Visit 16 after accountability is performed.

n: C-SSR to be completed if any positive responses from the Clinical Assessment of Suicidal Thinking and Behavior.

o: NPI-12 will be used if available, and both NPI-10 and NPI-12 scores calculated.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study with an Open-Label Extension Phase to Evaluate the Efficacy and Safety of Elenbecestat (E2609) in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat (E2609)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors (revised per Amendments 03 and 05):

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Neurology Business Group, Eisai Inc. — Date

INVESTIGATOR SIGNATURE PAGE

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IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 4.0

New version/date: Version 5.0/19 Jul 2018 (per Amendment 04)

Change	Rationale	Affected Protocol Sections
Addition of optional tau PET longitudinal substudy for study-eligible subjects from select geographical sites in the US (based on the proximity to the tau PET ligand manufacturing sites) who have an amyloid positive study-specific PET scan and consent to participate in the optional amyloid PET longitudinal substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620.	To allow for longitudinal assessment of brain tau pathology by tau PET in a substudy. Abnormal aggregation of tau in the brain is a factor in many neurodegenerative diseases, including Alzheimer's disease.	Synopsis • Objectives • Study Design • Assessments • Statistical Methods Section 5.3 Section 8.2 Figure 1 Section 9.1 Section 9.1.1 Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.5.1.4.2 Table 3 Table 4 Section 9.7.1.1.4 Section 9.7.1.7.3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 4)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 3 and Table 4)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and	Revised for clarification, since since CSF assessment of brain	Synopsis • Conduct of the Study

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	amyloid pathology will also include other biomarkers	• Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion criteria

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
		Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 4) Section 9.5.4.3.1 Section 10 Appendix 3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis – Statistical Methods • Bioanalytical Methods Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.4 Section 9.7.1.7.3
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 3)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 4)
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analysed.	PK analysis is no longer planned in subjects administed placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 1)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 3)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 5)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result documentation from the urine dipstick test needs to be retained as source documentation.	Added for clarification	Section 11.3
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted "pharmacogenomics (PGx)" data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Added new study director	To establish separate study directors in the 2 identical Phase 3 studies	PROTOCOL SIGNATURE PAGE
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4(new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 3 and Table 4) Section
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
has not resolved within 4 weeks.		
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1
Revidsed dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog_{14})	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for assessments; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 5
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 2 Section 9.5.2.1, Table 3

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 3), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have prothrombin time and INR	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
(derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 2 Section 9.5.2.1, Table 4
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study	Results of the special population hepatic impairment study (E2609-	Section 7.1

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	A001-103) with elenbecestat (E2609) have become available.	
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 3, and Table 4)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3, and Table 4)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 4)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 5)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 01)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01) V3.0 04 Apr 2017 (Amendment 02) V4.0 28 Jun 2017 (Amendment 03) V5.0 19 Jul 2018 (Amendment 04)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition14 (ADAS-cog14), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog14 Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid positron emission tomography (PET), volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or

dose increase of other AD pharmacotherapies

- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (International Shopping List Task [ISLT]). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the United States (US) who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main

study or participation in the amyloid PET or CSF substudies. (revised per Amendment 04)

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required to be performed during prerandomization. The tau PET scan is not an eligibility screening assessment as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendment 04) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for

eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarkeranalysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01 and 03) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both. (revised per Amendment 03) For those subjects who initially consent to both CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy will also be offered participation in the third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan, and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test

(females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will undergo additional assessments as indicated in the protocol. (revised per Amendments 01 and 04)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendment 04)

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24 month treatment period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 03) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core

Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
   b. CSF AD assessment(eg, Aβ(1-42), tau:Aβ(1-42) ratio) (revised per Amendment 03)

      NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who

consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03) The historical imaging data must be made available to the sponsor.

5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after

study drug discontinuation.)

- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence ofstroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund et al, 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 03)
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per

Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:
   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)
   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:
      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment,

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 03)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures

or safety.

- Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 01 and 03)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02) . Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with

study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02 and 03)

Blood will be collected to measure plasma PD (Aβ1-x) at Screening and various timepoints during treatment and followup. (revised per Amendments 01 02, and 03)

Amyloid PET imaging or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 03) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03)

Subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will receive assessments accordingly at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the ED visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendments 03 and 04) PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 02)

Exploratory biomarkers in CSF and/or plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 03)

T-tau and p-tau (neurodegenerative [NDG] biomarkers) in CSF, which are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), as well as plasma tau will be measured. NDG biomarkers have been demonstrated to increase in parallel with disease progression. (revised per Amendment 03)

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic

examinations; assessment of suicidality; and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test. (revised per Amendment 03) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period will require a more detailed follow-up. (revised per Amendment 03)

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF AD assessment (eg, Aβ [1-42], tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits. (revised per Amendment 03) Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be

measured using validated assays. (revised per Amendment 01)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 03)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment

with AChEI or memantine after randomization) by 24 months

- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at

24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. (revised per Amendment 04) Changes in clinical scales at 24 months will be the response variables and either continuous or

categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and

subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The

sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system

Abbreviation	Term
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier

Abbreviation	Term
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term

Abbreviation	Term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 03) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 03)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative, impartial witness, study partner). (revised per Amendment 03) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF), amyloid positron emission tomography (PET), and/or tau PET longitudinal substudies will also be asked to provide separate written consent for these procedures. (revised per Amendment 04)

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat (E2609) was administered orally by gavage once a day to male rats for 28 days prior to, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 03) Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. (revise dper Amendment 03)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment

crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 01)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat (E2609), tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline

of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). (revised per Amendments 01 and 03) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, CSF total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)
- To determine whether elenbecestat (E2609)is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609)is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate
- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

8.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)

- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study. A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have also consented to participate in the amyloid PET substudy. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. (revised per Amendment 04)

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration

of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

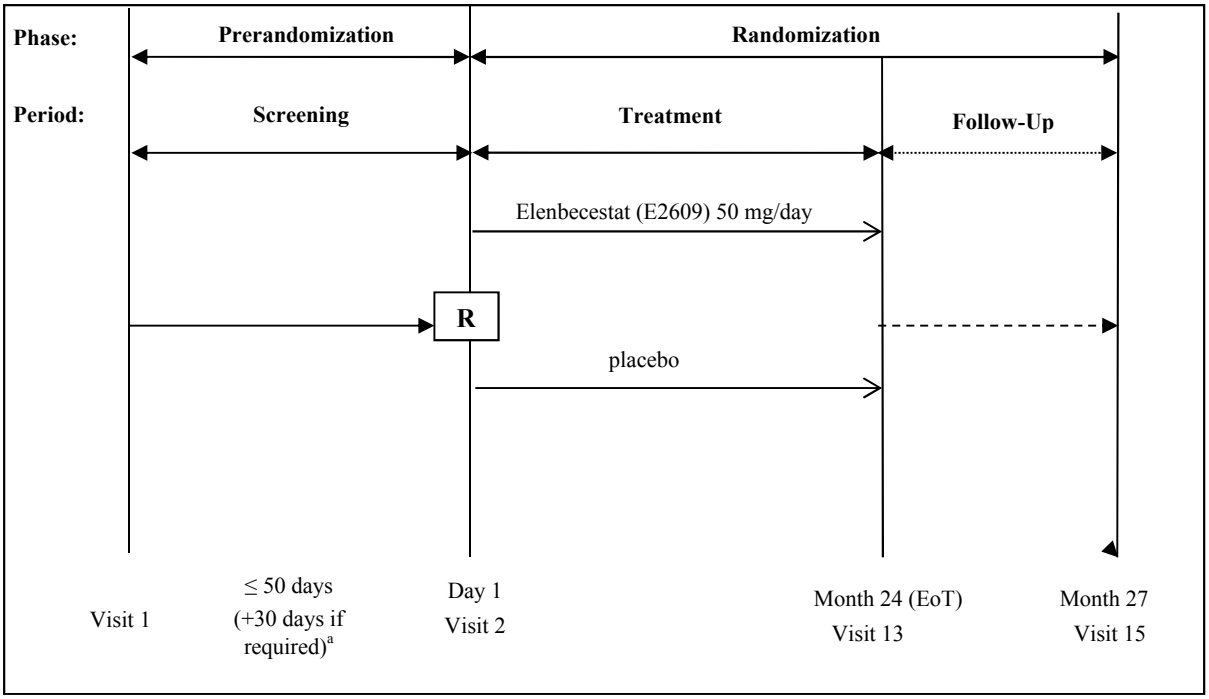

Figure 1 Study Design for E2609-G000-302

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, PET = positron emission tomography, R = randomization.

a. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. (revised per Amendment 04)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the

Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies. Subjects are able to consent to 1, 2, or all substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the amyloid PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01, 03, and 04)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in the optional tau PET longitudinal substudy, which will be conducted in Tier 5 of screening. (revised per Amendment 04)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to

progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 03)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 02 and 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need

to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment or both. (revised per Amendment 03) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those subjects who, in the opinion of the investigator, are not suitable for LP to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 03) For those subjects who consent to both CSF and amyloid PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who have consented to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy); the tau PET scan must take place at least 48 hours after the amyloid PET scan and at least 48 hours before randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Screening amyloid PET and/or Screening CSF AD assessment (eg, Aβ[1-42], tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. (revised per Amendment 03) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the lumbar puncture. Results of Screening amyloid PET scans conducted specifically for this study will also be valid for 90 days from the date of scanning for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical amyloid PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 03) For subjects who consent to the optional tau PET longitudinal substudy, the Screening tau PET scan will serve as the baseline data for the later tau PET scan. (revised per Amendment 04)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required prerandomization. The tau PET scan is not an eligibility screening assessment as the results do not influence randomization. There must be at least 48 hours between the tau PET scan and randomization. (revised per Amendments 03 and 04)

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET, tau PET, and/or CSF longitudinal substudies will receive assessments accordingly at 12 months (amyloid PET only), 24 months (all applicable substudy assessments), or at the early discontinuation (ED) visit (provided the subject has received at least 39 weeks of study drug and for subjects in the longitudinal amyloid PET substudy, provided that at least 6 months has elapsed since the prior amyloid PET scan was performed). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 01, 03, and 04) (Refer to Table 4 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03) Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as needed. (revised per Amendment 02) The results of some of the immunologic assessments will be

provided to the DSMB for periodic review during the study. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. (revised per Amendments 01, 03, and 04) Please refer to Schedule of Assessments (Table 4).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject

on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 03)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to

ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog_{14} immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical

meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on brain tau pathology at 24 months as measured by tau PET in a subset of subjects with EAD (revised per Amendment 04)
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months (revised per Amendment 04)
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on preserving connectivity (fMRI) at 24 months (revised per Amendment 04)
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

- To explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD (revised per Amendment 04)

CSF biomarkers,amyloid PET, and tau PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in substudies of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent. (revised per Amendment 04)

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 03)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 03) This second part is an optional longitudinal substudy.

Tau PET (revised per Amendment 04)

Tau PET imaging will be performed to evaluate the effects of elenbecestat (E2609) on brain tau pathology at 24 months. This will be assessed through a third optional longitudinal substudy that will be offered to subjects from select geographical sites (based on the proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. The tau PET data will also be used to evaluate the correlation between the effect of elenbecestat (E2609) on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months, and with the effect on preserving connectivity (fMRI) at 24 months. The tau PET data will also be used to explore the relationship between changes in brain amyloid levels (amyloid PET) and brain tau pathology (tau PET) at 24 months in subjects with EAD. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 01 and 02)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than

approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, Aβ(1-42), tau: Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03) The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of

treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must

agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 03)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy

      2) evidence of sustained virological response at least 12 weeks post-treatment

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 03)

    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

    - Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant

neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - elenbecestat (E2609)

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test. (revised per Amendment 03) If confirmed, study drug administration

should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 4) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 01 and 02) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 02)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 02)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 4 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 02) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia

staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 01 and 03)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02). Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet

drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)

- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 3 and Table 4. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the

state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog$_{14}$. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 02)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 3 and Table 4, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available at screening to determine subject eligibility for the study. (revised per Amendment 02 Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2.

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 03) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 3 and Table 4. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit and within a maximum of 1 week after the last dose of study drug. A trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendments 02 and 03)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 1 lists pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 03)

Table 1 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	Putative AD Diagnostic	PD	Exploratory Biomarker Subset	PD	Exploratory Biomarkers Subset
Whole Blood/ Plasma	ApoE [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)	PD	CSF AD Biomarkers	Exploratory Biomarkers (subset)
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)
a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 02 and 03)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 02 and 03)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 3 and Table 4. (revised per Amendment 02) The blood sample collected for PD analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 03)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation

(eg, treatment-emergent infection). (revised per Amendments 02 and 03) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 03) The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior amyloid PET scan was performed). (revised per Amendment 03) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening amyloid PET scans performed for this study (ie, historical amyloid PET scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Tau PET (revised per Amendment 04)

A third longitudinal biomarker substudy (tau PET) will be offered to study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites)

in the US who have an amyloid positive study-specific PET scan and who consent to participate in the amyloid PET substudy. For subjects who consent to the tau PET longitudinal substudy, tau PET imaging will be conducted during Screening (after amyloid positive PET results have been reported and before randomization) and again at 24 months (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order, but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure.

Descriptions and detailed instructions for all tau PET imaging can be found in the tau PET imaging manual provided to the study tau PET imaging facilities which will be in select geographical locations in the US, based on proximity to the tau PET ligand manufacturing sites. (revised per Amendment 04)

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 3 and Table 4); and MRIs as detailed in Table 3 and Table 4. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 3 and Table 4. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)

- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 4). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form during the Treatment Period and first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal

possible drug abuse potential, including physical dependency following discontinuation from study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). (revised per Amendment 03).

Euphoria-related terms: (revised per Amendment 03)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 03)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 03)

- Somnolence (revised per Amendment 03)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 03)

- Psychosis
- Aggression (revised per Amendment 03)
- Confusion and disorientation (revised per Amendment 03)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 03)

- Drug tolerance
- Habituation (revised per Amendment 03)
- Substance related disorders (revised per Amendment 03)

Physical dependence or withdraw (only for events observed within 14 days of the last dose of study drug): (revised per Amendment 03)

- Drug withdrawal syndrome (revised per Amendment 03)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 02)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize

the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. Table 3 and Table 4 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), rothrombin time, INR (derived from prothrombin time) and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 01 and 02). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing if required. (revised per Amendments 02 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 Vital Signs and Weight Measurements

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 3 and Table 4 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 Physical Examinations

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 4. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 3 and Table 4. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 02) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 4 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 3 and Table 4. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 3 and Table 4. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 4).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 3 and Table 4, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 02) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 032) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 4 presents the schedule of procedures/assessments for the Randomization Phase.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and amyloid and tau PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendmemnt 02)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 02)	X (Tier 5)
Tau PET (for longitudinal tau PET substudy baseline)[q] (revised per Amendment 04)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Subjects who participate in the optional longitudinal tau PET substudy will be permitted an additional window of up to 5 days (resulting in a total of up to 85 days) in order to accommodate the additional tau PET scan required to be performed during prerandomization. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization (revised per Amendments 03 and 04)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF, amyloid PET, and tau PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1, 2, or all substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid study-specific PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study). (revised per Amendment 04)

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase (revised per Amendment 04)

Phase	Prerandomization
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR derived from the prothrombin time, and aPTT are to be performed as part of Screening (revised per Amendments 01 and 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 03) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 02)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

n: Amyloid PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the amyloid PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal amyloid PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure. (revised per Amendment 04)

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and amyloid PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation. (revised per Amendment 04)

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

q: Study-eligible subjects from select geographical sites (based on proximity to the tau PET ligand manufacturing sites) in the US who have an amyloid positive study-specific PET scan and consent to participate in the amyloid PET substudy will also be offered participation in a third optional longitudinal substudy (tau PET substudy). Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. Participation in the tau PET substudy is optional and will require specific consent that will not affect enrollment or treatment in the main study or participation in the amyloid PET or CSF substudies. Subjects who participate in the optional longitudinal tau PET substudy will have up to 14 days to be randomized into the study from the reporting of the last screening eligibility assessment in order to accommodate the additional tau PET scan required pre-randomization. There must be at least 48 hours between the tau PET scan and randomization. If the subject has also consented to participate in the longitudinal CSF substudy, there must be at least 48 hours between each procedure (amyloid PET scan, tau PET scan and CSF collection) and between the last procedure and randomization. Only those subjects who have a study-specific amyloid positive PET scan and who have consented to both amyloid and tau PET substudies will be administered the tau PET tracer and scanned. (revised per Amendment 04)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (revised per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Tau PET (optional substudy) [u]												X	X			
Telephone contact[v]		X	X		X	X		X		X		X	X			
Blood samples for PK[w]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[x]	X	X	X		X	X		X		X		X	X	X	X	

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CSF sampling for PK and PD (optional substudy)[y]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[aa]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

d Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

e Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

f Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

g A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

h Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

i Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

j If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

k More frequent testing may be required per local regulations. (revised per Amendment 03) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

l Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

m Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 03)

n The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

o Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

p The clinical assessment of suicidality will require input from both the subject and the study partner

q There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

per Amendment 01)

r There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

s MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t Amyloid PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuroceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. An amyloid PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior amyloid PET scan was performed. (revised per Amendments 03 and 04)

u For subjects who consent to the tau PET longitudinal substudy, tau PET will be conducted at 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). At the 24 month timepoint (or at the ED visit), the amyloid and tau PET scans can be performed in either order but must be at least 48 hours apart. If the subject has also consented to the longitudinal CSF substudy, the longitudinal substudy assessments can be performed in any order, with at least 48 hours between each procedure. Tau PET scanning will be performed using a sponsor-supplied tau PET imaging agent, eg PI-2620. (revised per Amendment 04)

v Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

w Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

x PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 02 and 03)

y For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

z Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302 (Revised per Amendment 04)

Phase	Randomization															
Period	Treatment													Follow-Up		
Visit[a]	2	3	4	5	6	7	8	9	10	11	12	13	ED[b]	14[c]	15[c]	UNS Visit[d]
Day	1	15	29	57	85	183	274	365	456	547	638	729		757	813	
Week	1	3	5	9	13	27	40	53	66	79	92	105		109	117	
Weeks elapsed since 1st dose	0	2	4	8	12	26	39	52	65	78	91	104		108	116	
Nominal months elapsed since 1st dose	0		1	2	3	6	9	12	15	18	21	24		25	27	
Procedures/ Assessments																

[aa] AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 01 and 03)

[bb] The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03)

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 3 and Table 4 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 3). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 5 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 02) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 02)

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 02 and 03)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 03)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 02 and 03)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 02)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 02 and 03)	1	none	1×3.5 mL	none	3.5 mL

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening (revised per Amendments 02 and 03)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendment 03)	14		1×20 mL	13×20 mL	280 mL
Blood for immune status (revised per Amendment 03)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 01, 02, and 03)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendment 02)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendments 01 and 02)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 01, 02 and 03)		25.8 mL	46.8 mL	458.9 mL	531.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit) ; actual volume may vary based on local regulations. (revised per Amendment 02)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 03)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 03)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 4 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers AAβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability

criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, tau PET, CSF Aβ(1-x), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendments 03 and 04) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, or non-parametric methods if the data is not normally distributed, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. (revised per Amendment 04)

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in tau PET signal at 24 months (revised per Amendment 04)
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response

variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 03)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of

subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a

postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation))
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 01 and 03)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 03)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 03)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane

Listing 6 Permitted Medications

Zopiclone	(various)
Zolpidem	Ambien; others (revised per Amendment 03)

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 03)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 03)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation

Categories (revised per Amendment 03)			**Examples**[a]	
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 03)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 03)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere (revised per Amendment 03)	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 03)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 03)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 03)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 03)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 03) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors (revised per Amendment 03):

PPD

Neuroscience Business Group, Eisai Ltd.

Date

PPD

Neuroscience Business Group, Eisai Ltd.

Date

PPD

Neuroscience Business Group, Eisai,Ltd

Date

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Neuroscience Business Group, Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities	Added for consistency with Section 9.1.3.	Synopsis • Study Design
Specified duration of the Prerandomization Phase and that randomization should occur no more than 10 days after completion of all screening assessments/procedures and confirmation of eligibility	Added for clarification	Synopsis • Conduct of the Study Section 9.1.1 Section 9.1.2 Section 9.5.2.1 (Table 4)
Added that for any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) and the Clinical Dementia Rating (CDR) rater remain unchanged throughout the study.	Added to maximize consistency in diagnosis, disease staging and rating of the CDR.	Synopsis • Conduct of the Study Section 9.1.1.1.1 Section 9.1.2.1 Section 9.5.1.3.1 Section 9.5.2.1 (Table 3 and Table 4)
Removed pharmacodynamic (PD) blood specimen collection from the Screening Period and stipulated that Baseline blood draws for PD assessment will be performed predose at Visit 2 (Randomization Phase) rather than during Screening.	Revised for clarification	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that safety assessments of immune status will be performed throughout the study	Revised for clarification	Synopsis Conduct of the Study
Specified that the MMSE and CDR requirements are to be met at Screening	Revised for clarification	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Listed cerebrospinal fluid (CSF) amyloid beta (Aβ) (1-42) and tau:Aβ (1-42) ratio as examples of Alzheimer's disease (AD) biomarkers for brain amyloid pathology.	Revised for clarification, since since CSF assessment of brain amyloid pathology will also include other biomarkers	Synopsis • Conduct of the Study • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.2.4 Section 9.3.1
Added that positron emission tomography (PET) scans performed at the Early Discontinuation (ED) Visit should only be performed if 6 months has elapsed since the prior PET scan.	Added to define a minimal interval between PET scans for the PET longitudinal substudy.	Synopsis • Conduct of the Study • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.1.2 Section 9.1.2.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 4)
Specified that historical PET scans must have been positive for amyloid in order to be considered for eligibility purposes	Added for clarification	Synopsis • Inclusion Criteria • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.3.1
Added that subjects must have the capacity to provide informed consent (as determined in accordance with applicable professional standards and local laws/regulations) to enroll in the study.	Added for clarification based upon feedback from Health Authority(ies)	Synopsis • Inclusion Criteria Section 9.3.1

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the study partner must be literate.	Added for clarification	Synopsis • Inclusion criteria Section 9.3.1
Specified that findings of "diffuse" white matter disease "as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001)" on "central read" brain MRI findings at Screening are exclusionary. Clarified that evidence of multiple lacunar infarcts is exclusionary, regardless of region, whereas evidence of stroke is exclusionary when it involves a major vascular territory.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2 Section 10
Provided guidance for possible inclusion of subjects successfully treated for hepatitis C.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2
Specified that history of ophthalmic shingles or history of ocular herpes simplex virus infection are exclusionary, in addition to active infections of ophthalmic shingles or ocular herpes simplex virus.	Added for clarification	Synopsis • Exclusion criteria Section 9.3.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Removed "ocular" inflammatory disease requiring immunosuppressive or immunomodulatory therapy from exclusion criteria	Ocular therapy is permitted.	Synopsis • Exclusion criteria • Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7 Listing 2 of Appendix 2
Removed exclusion for significant abnormalities in laboratory tests or electrocardiogram (ECG) at Baseline assessment	Results from Baseline assessment will not be available at the Baseline Visit	Synopsis • Exclusion Criteria Section 9.3.2
Clarified that the exclusion of subjects with a prolonged QTcF interval is based on the central read of the Screening ECG.	Added for clarification	Synopsis • Exclusion Criteria Section 9.3.2
Specified that "short-term" concomitant use of benzodiazepines is permitted as specified in the protocol	Added for clarification	Synopsis • Concomitant Drug/ Therapy Section 9.4.7 Listings 5 and 6 of Appendix 2
Specified that repeat testing for subjects who develop Grade 2 or greater lymphocytopenia should be performed as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test result.	Added for clarification	Synopsis • Safety Assessments Section 9.3.3
Updated text describing monitoring adverse events (AEs) that may signal drug abuse potential, physical withdrawal or dependence; specified that monitoring will include the Treatment Period and the first 4 weeks of the Follow-up Period	Added for clarification and alignment with current US Food and Drug Administration (FDA) Guidance for Industry for "Assessment for Abuse Potential for Drugs"	Synopsis • Safety Assessments Section 9.5.1.5.1 Section 9.5.2 (Table 4) Section 9.5.4.3.1 Section 10 Appendix 3

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that of apolipoprotein E (*ApoE*) and N-acetyltransferase 2 (NAT2) genotype analyses will be performed using validated assays	Added for clarification	Synopsis – Statistical Methods • Bioanalytical Methods Section 9.5.1.4.2
Deleted Aβ(1-40) from biomarker endpoints and assessments	Analysis of the biomarker is no longer planned as a primary biomarker endpoint	Synopsis • Biomarker Endpoints • Analyses for Biomarker Endpoints Section 9.5.1.4.2 Section 9.7.1.1.4 Section 9.7.1.7.3
Deleted instructions for subjects unable to read the informed consent, since illiteracy is an exclusion criterion	Removed for consistency with exclusion criterion 13	Section 5.3
Added that the Investigator shall reassess consent capacity at periodic intervals during the subject's involvement in the study and that the investigator must obtain subject assent and consent by the legal representative (in accordance with local laws and regulations) for subjects who lose the capacity to provide informed consent during the study.	Clarification based upon feedback from Health Authority(ies)	Section 5.3
Deleted reference to "in progress" status of the report for Study E2609-A001-003 and "preliminary" nature of data for Study E2609-A001-103	Clinical study reports are now final for both	Section 7.1
Specified that there are no contraceptive requirements for male subjects and that there is no requirement to follow partner pregnancies, based on in vivo nonclinical data..	Clarification based upon feedback from Health Authority(ies) and Ethics Committees	Section 7.1 Section 9.5.4.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Provided duration of validity for screening Magnetic Resonance Imaging (MRI), amyloid PET and CSF assessments	Added for clarification regarding whether or not a rescreened subject needs to have these assessments repeated.	Section 9.1.1.1.4 Section 9.1.1.1.5
Specified that the 10 day period between completion of screening and randomization at Visit 2 starts with the reporting of the final screening assessment, which in most cases will be the confirmation of amyloid pathology	Added for clarification	Section 9.1.2 Section 9.5.2.1 (Table 3)
Provided a minimum recommended observation period following the first dose of study drug	Clarification based upon feedback	Section 9.1.2.1 Section 9.5.2.1 (Table 4)
Deleted reference to the non-amyloidogenic secretase pathway.	Alpha secretase is not evaluated in this study	Section 9.2.1
Deleted reference to whole brain analysis (the average of 5-6 cortical regions) and brain region analysis.	These analyses are not planned	Section 9.2.4
Deleted text indicating that a predetermined percentage of pharmacokinetic (PK) blood samples from placebo subjects will be analysed.	PK analysis is no longer planned in subjects administed placebo.	Section 9.5.1.4.1
Added a table listing the planned pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments	Added for clarification	Section 9.5.1.4.2 (Table 1)
Deleted assessment of beta-amyloid converting enzyme 1 (BACE1) levels as a planned analysis	A validated BACE1 assay has not been established; exploratory assessments may be performed	Section 9.5.1.4.2

Revisions to Version 3.0

New version/date: Version 4.0/28 Jun 2017 (per Amendment 03)

Change	Rationale	Affected Protocol Sections
Added that the blood sample collected at screening for determination of *ApoE* genotype is mandatory and that a subset of subjects will also be evaluated for NAT2 genotype.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.2
Removed Tier 3 collection of blood sample for immunologic assessments, including isolation of PBMCs for storage at Screening	Collection and storage will begin at Visit 2	Section 9.5.2.1 (Table 3)
Added a separate column to the blood volume table for Visit 2 (Baseline) and revised specimen volume values	Added for clarification	Section 9.5.2.2 (Table 5)
The definition of a treatment-emergent adverse event (TEAE) was revised to specify emergence "on or after the start of study treatment"	Added for clarification	Section 9.7.1.8.2
Specified that only the test result documentation from the urine dipstick test needs to be retained as source documentation.	Added for clarification	Section 11.3
Itraconazole was added to the prohibited medications	Itraconazole is a strong inhibitor of carboxylesterase 2 (CES2)based on in vitro studies	Listing 1 of Appendix 2
Added a trade name for zolpidem	Added for clarification	Listings 6 of Appendix 2
Deleted "pharmacogenomics (PGx)" data from the description of individual subject data that may be returned to them or their physicians	Due to the blinded nature of the study design, this data will not be disclosed	Appendix 4.
Added new study director	To establish separate study directors in the 2 identical Phase 3 studies	PROTOCOL SIGNATURE PAGE
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4(new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 3 and Table 4) Section
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Revised text to include cerebrospinal fluid (CSF) for description of exploratory biomarkers	Corrected missing information	Section 9.2.4
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
has not resolved within 4 weeks.		
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1
Revidsed dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog_{14})	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for assessments; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 5
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 2 Section 9.5.2.1, Table 3

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 3), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have prothrombin time and INR	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 2) Section 9.5.2.1 (Table 3 and Table 4)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
(derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 2 Section 9.5.2.1, Table 4
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study	Results of the special population hepatic impairment study (E2609-	Section 7.1

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	A001-103) with elenbecestat (E2609) have become available.	
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 3, and Table 4)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3, and Table 4)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 3 and Table 4)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 4)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 5)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 01)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01) V3.0 04 Apr 2017 (Amendment 02) V4.0 28 Jun 2017 (Amendment 03)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid positron emission tomography (PET), volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (International Shopping List Task [ISLT]). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 03) Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03) All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic

criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. Similarly, every effort should be made to ensure that for any given subject, the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory tests, AD exploratory biomarkeranalysis, and mandatory pharmacogenomics (PGx) analysis of *ApoE* genotype. A subset of PGx specimens may also be tested for N-acetyltransferase 2 (NAT2). (revised per Amendments 01 and 03) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both. (revised per Amendment 03) For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 01)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Blood for PD (Aβ(1-x)), exploratory biomarkers, and PK assessments will be performed during the 24 month treatment period. (revised per Amendment 04)

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, assessments of immune status, and centrally-read ECGs will be performed throughout the 24 months of treatment in the study. (revised per Amendment 03) Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose

of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.

b. CSF AD assessment(eg, Aβ(1-42), tau:Aβ(1-42) ratio) (revised per Amendment 03)

NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03) The historical imaging data must be made available to the sponsor.

5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with applicable professional standards and local laws/regulations). (revised per Amendment 03)

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test). A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

    - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
        - total abstinence (if it is their preferred and usual lifestyle)

- an intrauterine device or intrauterine hormone-releasing system
- an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
- have a vasectomized partner with confirmed azoospermia.

- Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
   - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence ofstroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund et al, 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 03)
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or

C). Any 2 of the following criteria at Screening would exclude the subject: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

      1) evidence of treatment with direct antiviral combination therapy
      2) evidence of sustained virological response at least 12 weeks post-treatment,

      The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 03)
    - A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:
    - Physical examination or vital signs at Screening or Baseline that in the opinion of the

investigator require further investigation or treatment or may interfere with study procedures or safety.

- Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)
- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)

b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 01 and 03)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02) . Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with

study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood samples will be obtained at Screening and will be used for assessment of putative AD diagnostics and to determine the *ApoE* genotype of all subjects and NAT2 in a subset of subjects enrolled in this study. (revised per Amendments 01, 02 and 03)

Blood will be collected to measure plasma PD (Aβ1-x) at Screening and various timepoints during treatment and followup. (revised per Amendments 01 02, and 03)

Amyloid PET imaging or CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) or both will be used to confirm that all study subjects have amyloid deposition in the brain. (revised per Amendment 03) This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid positive PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03)

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug [and at least 6 months has elapsed since the prior PET scan was performed for subjects in the longitudinal PET substudy). (revised per Amendment 03) PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 02)

Exploratory biomarkers in CSF and/or plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 02 and 03)

T-tau and p-tau (neurodegenerative [NDG] biomarkers) in CSF, which are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), as well as plasma tau will be measured. NDG biomarkers have been demonstrated to increase in parallel with disease progression. (revised per Amendment 03)

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count should be repeated as soon as possible, with the repeat blood sample drawn no later than 5 calendar days from the date of the original test. (revised per Amendment 03) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period will require a more detailed follow-up. (revised per Amendment 03)

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF AD assessment (eg, Aβ [1-42], tau:Aβ [1-42] ratio) will be performed for eligibility and treatment response in consenting subjects using validated, commercially available kits. (revised per Amendment 03) Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be

measured using validated assays. (revised per Amendment 01)

The *ApoE* genotype for all subjects and NAT2 genotype in a subset of subjects will be determined from blood specimens using validated assays. (revised per Amendment 03)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment

with AChEI or memantine after randomization) by 24 months

- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at

24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ)

and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and

subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative

O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BDNF	brain-derived neurotrophic factor
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CD33	sialic acid binding immunoglobulin-like lectin 3 (Siglec-3)
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system

Abbreviation	Term
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EPHA1	erythropoietin-producing hepatoma receptor A1
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier

Abbreviation	Term
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NDG	neurodegenerative
NAT2	N-acetyltransferase 2
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term

Abbreviation	Term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
RNA	ribonucleic acid
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
TREM2	triggering receptor expressed on myeloid cells 2
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary
YKL-40	human cartilage glycoprotein-39 (HC gp-39)

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should be capable of reading and understanding the statement before signing and dating it and will be given a copy of the signed document. The subject should read the ICF and any other written information provided and be given the opportunity to ask questions so the information can be explained to the subject, as needed. After the subject has orally consented to participate in the study and has personally signed and dated the ICF, the study team member who conducted the consent should personally sign and date the consent form. (revised per Amendment 03) No subject can enter the study before his/her informed consent has been obtained.

The subject's capacity to consent must be assessed at periodic intervals during the course of the subject's involvement in the study, including whenever any concern is expressed about the subject's continued capacity to consent (eg, by the study partner or a subject's family member). The method and frequency of the assessment of capacity to consent must be performed in accordance with applicable professional standards and local laws/regulations. During the course of the study, should a subject, in the investigator's opinion, decline to the point of lacking capacity to consent, the investigator should obtain the assent of the subject and the consent of their designated representative per the applicable local laws/regulations and IRB/IEC standards in order for the subject to continue in the study. (revised per Amendment 03)The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia

Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local laws and regulations and professional standards. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties (eg, investigator/study team member conducting the consent, study subject, legally acceptable representative, impartial witness, study partner). (revised per Amendment 03) The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. An oral fertility and early embryonic development study in male rats has been conducted, in which elenbecestat (E2609) was administered orally by gavage once a day to male rats for 28 days prior to, and throughout the mating period, at doses of 30, 100, or 300 mg/kg. There were no effects on mating, fertility, and early embryonic development at any dose level. The NOAEL was 100 mg/kg for male general toxicity and 300 mg/kg for male reproduction in this study. Therefore, there are no contraceptive requirements for male subjects participating in this study. (revised per Amendment 03) Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. (revise dper Amendment 03)

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment

crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 01)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat (E2609), tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline

of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow N-acetyltransferase 2 (NAT2) genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). (revised per Amendments 01 and 03) However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609)is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609)is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase starts with consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03) Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic

criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1.

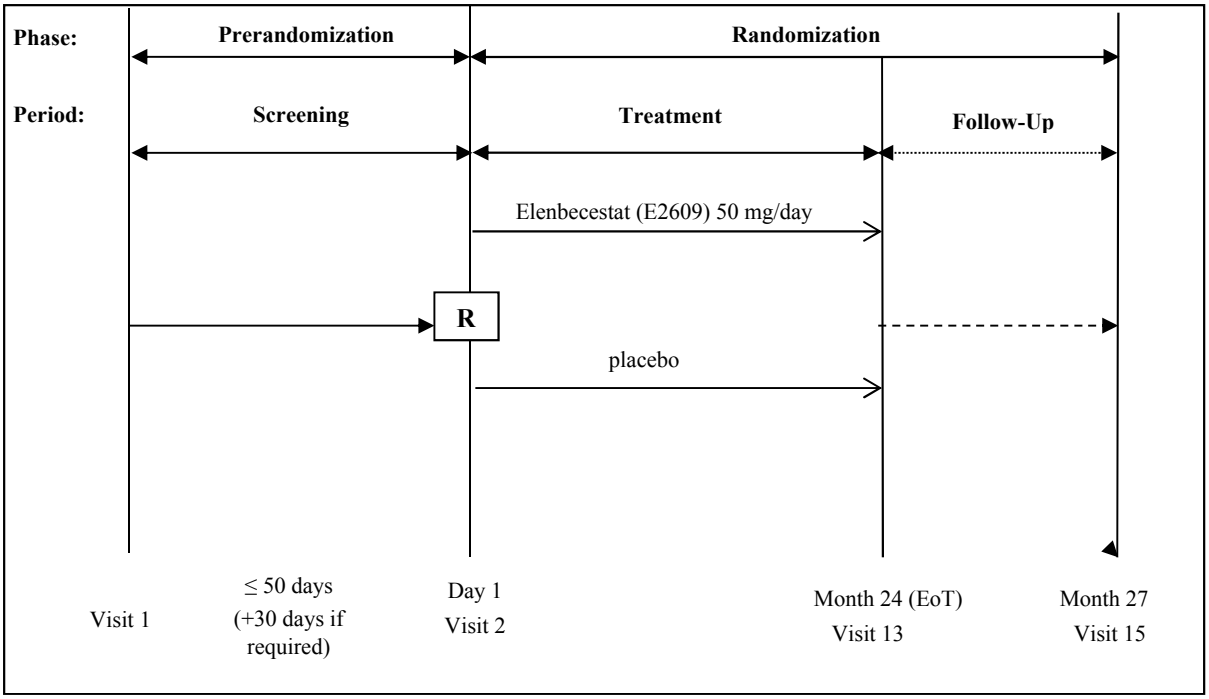

Figure 1 Study Design for E2609-G000-302

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase starts with signed informed consent and ends with randomization, and has a duration of up to 50 days (plus an additional window of up to 30 days if required). (revised per Amendment 03)

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study.

Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging by central review will not be required in order for the subject to progress to Tier 2 of the Screening Visit, but will be required before the subject progresses to Tier 4. (revised per Amendment 03)

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, AD diagnostic/exploratory biomarkers, and for immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing and/or evaluation of lymphocyte subsets as required. (revised per Amendments 02 and 03) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures. Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF AD assessment or both. (revised per Amendment 03) Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) Amyloid PET screens will be performed according to local regulatory guidelines and may be restricted for those

subjects who, in the opinion of the investigator, are not suitable for LP to assess CSF eligibility (ie, evidence of amyloid pathology). (revised per Amendment 03) For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Screening amyloid PET and/or Screening CSF AD assessment (eg, Aβ[1-42], tau:Aβ(1-42) ratio) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. (revised per Amendment 03) Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies. Results of Screening CSF AD assessments will be valid for 90 days from the date of the lumbar puncture. Results of Screening PET scans conducted specifically for this study will also be valid for 90 days from the date of scanning for the longitudinal substudy. These assessments will not need to be repeated should the subject be randomized within that time period, either under their original subject identification number or under a new re-screening subject identification number. Historical PET scans used for determination of eligibility only (ie, not used for the longitudinal substudy) are valid for 12 months. (revised per Amendment 03)

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03)

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol (PET scans performed at ED should have a 6 months gap from the previous PET scan). Note that subjects who are assessed by both amyloid PET and CSF AD assessment (eg, Aβ(1-42), tau:Aβ(1-42) ratio) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) (Refer to Table 4 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03) Inclusion and exclusion criteria will again be reviewed together with

concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for PD/exploratory biomarkers and immunologic assessments. (revised per Amendment 03) Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as needed. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03) Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 03) For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendments 01 and 03) Please refer to Schedule of Assessments (Table 4).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed exploratory biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and neurodegenerative (NDG) changes correlating these with clinical benefit. An additional analysis will evaluate whether

inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. (revised per Amendment 03)

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects

(Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF Aβ levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau and/or tau: Aβ(1-42) ratios will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects. (revised per Amendment 03)

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method of confirming the presence of amyloid pathology is CSF assessment); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months. (revised per Amendment 03) This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur

preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 01 and 02)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following at Screening: (revised per Amendment 03)
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.

4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF AD assessment (eg, Aβ(1-42), tau: Aβ(1-42) ratio) (revised per Amendment 03)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid positive PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. (revised per Amendment 03) The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must be literate and able to provide written informed consent. (revised per Amendment 03) In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.
9. Provide written informed consent. Subjects must, in the investigator's judgment, have the capacity to consent (capacity to consent should be determined in accordance with

applicable professional standards and local laws/regulations). (revised per Amendment 03)

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

- Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

- Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

    - Exhibit other significant pathological findings on central read of the brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts; evidence of stroke involving a major vascular territory; severe small vessel or diffuse white matter disease as defined by a score of 3 on the age-related white matter changes scare (Wahlund, et al., 2001); space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary). (revised per Amendment 03)

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:

    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendment 01)

    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

- Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

- Subjects with chronic viral hepatitis. Subjects with a history of chronic viral hepatitis C may be included if they meet the following requirements:

  1) evidence of treatment with direct antiviral combination therapy

  2) evidence of sustained virological response at least 12 weeks post-treatment

  The inclusion of subjects with a history of chronic viral hepatitis C must be discussed and agreed with the Medical Monitor. (revised per Amendment 03)

- A history of active tuberculosis disease (TB), a history of ophthalmic shingles or a history of ocular herpes simplex virus (HSV) infection (revised per Amendment 03)

- Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic immunosuppressive or immunomodulatory therapy. (revised per Amendment 03)

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

- Physical examination or vital signs at Screening or Baseline that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

- Laboratory tests or ECG at Screening that in the opinion of the investigator require further investigation or treatment or may interfere with study procedures or safety. (revised per Amendment 03)

- Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)

- Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms according to central reading at Screening). (revised per Amendment 03) If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - elenbecestat (E2609)

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), the absolute lymphocyte count test should be repeated as soon as possible with the repeat blood sample drawn no later than 5 calendar days from the date of the original test. (revised per Amendment 03) If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 4) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 01 and 02) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 02)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any

infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 02)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 4 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The

randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 02) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)
b) Systemic immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendments 01 and 03)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02). Subjects who start on AChEI or memantine

or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including short-term use of benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing. (revised per Amendment 03)

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement

- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study

drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 3 and Table 4. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild

AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog$_{14}$. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 02)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 3 and Table 4, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine

the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available at screening to determine subject eligibility for the study. (revised per Amendment 02 Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2.

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609). Samples from all subjects receiving active treatment will be analyzed. Placebo samples will be held in storage in the event that confirmatory analysis is requested. (revised per Amendment 03) Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 3 and Table 4. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have

stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit and within a maximum of 1 week after the last dose of study drug. A trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendments 02 and 03)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Table 1 lists pharmacodynamic, pharmacogenomic, and exploratory biomarker assessments. Key elements of these assessments are described below. (revised per Amendment 03)

Table 1 Planned Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Sample	Screening		Baseline		Treatment/Follow-up	
	PGx	**Putative AD Diagnostic**	**PD**	**Exploratory Biomarker Subset**	**PD**	**Exploratory Biomarkers Subset**
Whole Blood/ Plasma	ApoE [a] NAT2 [b] TREM2 [b] CD33 [b] EPHA1 [b]	microRNA tau:Aβ(1-42) ratio Aβ oligomers	Aβ(1-x)	NFL VILIP1 YKL-40 Tau	Aβ(1-x)	NFL VILIP1 YKL-40 tau

Sample	Eligibility	Baseline (CSF Substudy)			Treatment/Follow-up (CSF Substudy)		
	CSF AD Biomarkers	**PD**	**CSF AD Biomarkers**	**Exploratory Biomarkers (subset)**	**PD**	**CSF AD Biomarkers**	**Exploratory Biomarkers (subset)**
CSF	Aβ(1-42) Tau:Aβ(1-42) ratio	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1	Aβ(1-x)	Aβ(1-42) tau p-tau **(Subset)** Aβ isoforms Aβ(1-40) Aβ(1-38)	NFL VILIP1 YKL-40 BDNF BACE1

Aβ = amyloid beta, Aβ(1-x) = amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42]), AD = Alzheimer's disease, *ApoE* = apolipoprotein E, BACE1 = beta-amyloid converting enzyme 1, BDNF = brain-derived neurotrophic factor, CD33 = sialic acid binding immunoglobulin-like lectin 3 (Siglec-3), CSF = cerebrospinal fluid, EPHA1 = erythropoietin-producing hepatoma receptor A1, NAT2 = N-acetyltransferase 2, NFL = neurofilament light, PD = pharmacodynamic, PGx = pharmacogenomics, RNA = ribonucleic acid, TREM2 = triggering receptor expressed on myeloid cells 2, VILIP1 = visinin like protein 1, YKL-40 = human cartilage glycoprotein-39 (HC gp-39)

a: mandatory for all subjects
b: to be analyzed in a subset of subjects

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), t-tau, and p-tau. (revised per Amendments 02 and 03)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), t-tau, and p-tau will be performed using commercially available ELISAs. (revised per Amendments 02 and 03)

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 3 and Table 4. (revised per Amendment 02) The blood sample collected for PD analyses at Visit 2 should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day. (revised per Amendment 03)

Prerandomization blood samples for immunologic assessments and CSF (if applicable) will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendments 02 and 03) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. NAT2 genotype will be evaluated in a subset of subjects. Genotype will be determined from blood specimens using validated assays. (revised per Amendment 03) The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are

considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug and at least 6 months has elapsed since the prior PET scan was performed). (revised per Amendment 03) Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 3 and Table 4); and MRIs as detailed in Table 3 and Table 4. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 3 and Table 4. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease

- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 4). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that may signal drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form during the Treatment Period and first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. This includes AEs listed below. Examples of such AEs are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. This additional follow-up of AEs that signal possible drug abuse potential, including physical dependency following discontinuation from

study drug, is in line with current FDA Guidance for Industry for "Assessment for Abuse Potential for Drugs" (FDA 2017 Abuse Potential Guidelines). (revised per Amendment 03).

Euphoria-related terms: (revised per Amendment 03)

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Dizziness (revised per Amendment 03)
- Thinking abnormal
- Hallucination
- Inappropriate affect

Terms indicative of impaired attention, cognition, and mood: (revised per Amendment 03)

- Somnolence (revised per Amendment 03)
- Mood disorders and disturbances

Dissociative/psychotic terms (revised per Amendment 03)

- Psychosis
- Aggression (revised per Amendment 03)
- Confusion and disorientation (revised per Amendment 03)
- Dissociative state

Related terms not captured elsewhere: (revised per Amendment 03)

- Drug tolerance
- Habituation (revised per Amendment 03)
- Substance related disorders (revised per Amendment 03)

Physical dependence or withdraw (only for events observed within 14 days of the last dose of study drug): (revised per Amendment 03)

- Drug withdrawal syndrome (revised per Amendment 03)

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 02)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize

the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 2. Subjects should be in a seated or supine position during blood collection. Table 3 and Table 4 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 2 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), rothrombin time, INR (derived from prothrombin time) and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 01 and 02). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing if required. (revised per Amendments 02 and 03) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 3 and Table 4 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 4. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 3 and Table 4. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 02) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 4 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 3 and Table 4. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 3 and Table 4. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 4).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 3 and Table 4, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 02) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 032) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be further tested in the event that a subject develops AEs that warrant investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 3 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 4 presents the schedule of procedures/assessments for the Randomization Phase.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PGx[i]	X (Tier 3)
Blood samples for AD diagnostics and exploratory biomarkers[j] (revised per Amendmemnt 02)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (randomization is to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required) (revised per Amendment 03)	
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 02)	X (Tier 5)

NOTES:

Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.

All screening assessments and randomization are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after reporting of the last screening assessment (for most subjects, this will be the amyloid eligibility assessment). (revised per Amendment 03)

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PGx = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study).

b: For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit. For any given subject, every effort should be made to ensure that the CDR rater remains unchanged throughout the study. (revised per Amendment 03)

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR derived from the prothrombin time, and aPTT are to be performed as part of Screening (revised per Amendments 01 and 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. (revised per Amendment 03) For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 02)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: Results of the Screening MRI will be valid for 90 days from the date of scanning. The MRI will not need to be repeated should the subject be randomized within that time period either under their original subject identification number or under a new re-screening subject identification number. (revised per Amendment 03)

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure.

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.
Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (revised per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog_{14}[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI_{10}	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[w]	X	X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional												X	X			

Table 4 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
substudy)[x]																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] More frequent testing may be required per local regulations. (revised per Amendment 03) If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory analyses, in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents. (revised per Amendment 03)

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. For any given subject, every effort should be made to ensure that the diagnosing clinician (responsible for the initial diagnosis and for disease staging) remains unchanged throughout the study. (revised per Amendment 03) This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent (eg, Neuroceq, if available) or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks and at least 6 months has elapsed since the prior PET scan was performed. (revised per Amendment 03)

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 2, 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. (revised per Amendments 02 and 03)

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that may signal drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire). Similarly, AEs reported during the first 4 weeks following the last dose of study drug that might indicate physical dependency also require a more detailed follow-up through completion of the same eCRF form. Categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3 and a more comprehensive list is provided in the eCRF Completion Guidelines. (revised per Amendments 01 and 03)

[aa] The first dose of study drug will be given to the subject at the study site. Subjects will be encouraged to stay at the site for observation for at least 30 minutes following their first dose of study drug. The duration of this observation period can be extended at the Investigator's discretion, eg, if warranted by medical history or concomitant medication. (revised per Amendment 03)

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 3 and Table 4 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 3). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 5 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 02) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 02)

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Blood					
Clinical chemistry (revised per Amendments 02 and 03)	15	1×2.5 mL	1×2.5 mL	13×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	0	can use blood drawn for clinical chemistry	can use blood drawn for clinical chemistry	none	no additional volume
Hematology (revised per Amendment 03)	15	1×2 mL	1×2 mL	13×2 mL	30 mL
Coagulation (revised per Amendments 02 and 03)	15	1×1.8 mL	1×1.8 mL	13×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 02)	1	1×2.5 mL	none	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendments 02 and 03)	1	none	1×3.5 mL	none	3.5 mL

Table 5 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)			Total Volume[a] (mL)
		Screening Visits	Visit 2 Baseline (predose) (revised per Amendment 03)	Treatment and Follow-Up Periods	
Vitamin B12 at Screening (revised per Amendments 02 and 03)	0	can use blood drawn for TFT	none	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing (revised per Amendment 03)	14		1×20 mL	13×20 mL	280 mL
Blood for immune status (revised per Amendment 03)	8	none	1×5 mL	7×5 mL	40 mL
AD diagnostics and exploratory biomarker (revised per Amendment 03)	1	1×6 mL	none	none	6 mL
PD and exploratory biomarker sample (revised per Amendments 01, 02, and 03)	10	none	1×12 mL	9×6 mL	66 mL
PK analysis (revised per Amendment 02)	7	none	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendments 01 and 02)	1	1×6 mL	none	none	6 mL
All blood samples, total volume collected (revised per Amendments 01, 02 and 03)		25.8 mL	46.8 mL	458.9 mL	531.5 mL
CSF					
Amyloid eligibility	1	1×12 mL	none	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	none	1×12 mL	12 mL

Note: Actual volumes may be less, based on regional differences in Central Laboratories.
AD = Alzheimer's disease, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.
a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit) ; actual volume may vary based on local regulations. (revised per Amendment 02)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

Pregnancies in partners of male study subjects do not need to be reported. (revised per Amendment 03)

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects

Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

Subjects will be monitored for AEs that may signal drug abuse potential during the Treatment Period and the first 4 weeks of the Follow-up Period. Examples of AEs that may signal drug abuse potential are provided in Appendix 3. A detailed listing of AEs that may signal drug abuse potential is provided in the E2909-G000-301 eCRF Completion Guidelines. (revised per Amendment 03)

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 4 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have ‘completed’ the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers AAβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.

- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF Aβ(1-x), t-tau, p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. (revised per Amendment 03) Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-42), and Aβ(1-x) at 24 months (revised per Amendment 03)
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges on or after start of study treatment, having been absent at pretreatment (Baseline) or
- Reemerges on or after start of study treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity on or after start of study treatment relative to the pretreatment state, when the AE is continuous. (revised per Amendment 03)

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or

severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When

displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-stick test result documentation))
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil
Itraconazole (revised per Amendment 04)

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendments 01 and 03)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical, ocular, and inhaled formulations with minimal systemic exposure need not be prohibited. (revised per Amendment 03)

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which Are Not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 03)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines (short-term use only, [ie, 2 to 4 weeks]) and sedatives (revised per Amendment 04)	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane

Listing 6 Permitted Medications

Zopiclone	(various)
Zolpidem	Ambien; others (revised per Amendment 03)

PRN = Pro re nata

Appendix 3 Examples of AEs That May Signal Drug Abuse Potential

Categories (revised per Amendment 03)			**Examples**[a]	
Euphoria-related terms (revised per Amendment 03)	**1**	**Euphoric mood**	Euphoric mood	Feeling high
			Euphoria	Felt high
			Euphoric	High
			Exaggerated well-being	High feeling
			Excitement excessive	Laughter
	2	**Elevated mood**	Elevated mood	Elation
			Mood elevated	
	3	**Feeling abnormal**	Feeling abnormal	Funny episode
			Cotton wool in head	Fuzzy
			Feeling dazed	Fuzzy head
			Feeling floating	Muzzy head
			Feeling strange	Spaced out
			Feeling weightless	Unstable feeling
			Felt like a zombie	Weird feeling
			Floating feeling	Spacey
			Foggy feeling in head	
	4	**Feeling drunk**	Feeling drunk	Intoxicated
			Drunkenness feeling of	Stoned
			Drunk-like effect	Drugged
	5	**Feeling of relaxation**	Feeling of relaxation	Relaxed
			Feeling relaxed	Increased well-being
			Relaxation	Excessive happiness
	6	**Dizziness**	Dizziness	
	7	**Thinking abnormal**	Thinking abnormal	Thinking disturbance
			Abnormal thinking	Thought blocking
			Thinking irrational	Wandering thoughts
	8	**Hallucination**	Hallucination	Floating
			Illusions	Rush
			Flashbacks	Feeling addicted
	9	**Inappropriate affect**	Elation inappropriate	Inappropriate elation

Categories (revised per Amendment 03)			**Examples**[a]	
			Exhilaration inappropriate	Inappropriate laughter
			Feeling happy inappropriately	Inappropriate mood elevation
			Inappropriate affect	
Terms indicative of impaired attention, cognition, and mood (revised per Amendment 03)	**10**	**Somnolence**	Somnolence	
	11	**Mood disorders and disturbances**	Mental disturbance	Mood swings
			Depersonalisation	Emotional lability
			Psychomotor stimulation	Emotional disorder
			Mood disorders	Emotional distress
			Emotional and mood disturbances	Personality disorder
			Delirium	Impatience
			Delirious	Abnormal behavior
			Mood altered	Delusional disorder
			Mood alterations Mood instability	Irritability
Dissociative/psychotic terms (revised per Amendment 03)	**12**	**Psychosis**	Psychosis	Psychotic episode or disorder
	13	**Aggression**	Aggression	
	14	**Confusion and disorientation**	Confusion and disorientation	
	15	**Dissociative State**	Dissociation	Detached
			Disconnected	Sensation of distance from one's environment
			Derealisation	Loss of a sense of personal identity
			Depersonalisation	
Related terms not captured elsewhere (revised per Amendment 03)	**16**	**Drug tolerance**	Drug tolerance	
	17	**Habituation**	Habituation	
	18	**Substance related disorders**	Substance-related disorders	
Physical Dependence or Withdraw[b] (revised per Amendment 03)	**18**	**Drug withdrawal syndrome**	Drug withdrawal syndrome	Chills
			Headache	Decreased concentration
			Anxiety	Agitation
			Nausea	Irritability
			Vomiting	Sleep disturbances
			Tremor	Mood changes

a: Examples include terminology provided in the following guidance: U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry. Assessment of Abuse Potential of Drugs. January 2017. The same term may apply to more than 1 category. A more comprehensive list of terms is provided in the eCRF Completion Guidelines. (revised per Amendment 03)
b: Only for events observed within the first 4 weeks of last dose of study drug. (revised per Amendment 03)

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the subjects or their family members. Therefore, these results will not be disclosed to the subjects or their physicians. (revised per Amendment 03)

If at any time, PD and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. (revised per Amendment 03) Sharing of research data with individual subjects should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors (revised per Amendment 03):

PPD

Eisai Ltd.

Date

PPD

Eisai Ltd.

Date

PPD

Eisai, Inc.

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Added that the start of the open-label Extension Phase will require a protocol amendment with prior approval from applicable Health Authorities.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Extension Phase Section 9.1.3
Added that the end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Study Design Section 9.1.4(new)
Extended the requirement of compliance with local standard of care for concomitant use of acetylcholinesterase inhibitor (AChEI) or memantine for symptomatic treatment of Alzheimer's disease (AD) to include initiation or changing dose of AChEI or memantine during the study.	Clarification based upon feedback from Health Authority(ies)	Synopsis • Concomitant Drug/Therapy Section 9.4.7
Revised description of blood/CSFcollection and assay for pharmacodynamic (PD) and exploratory biomarkers.	Added for clarification	Synopsis • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments Section 9.5.1.4.1 Section 9.5.1.4.2 Section 9.5.2.1 (Table 2 and Table 3) Section
Specified that peripheral blood mononuclear cells (PBMCs) will be stored for testing as required.	Added for clarification	Section 9.1.1.1.3 Section 9.1.2.1
Revised text to include cerebrospinal fluid (CSF) for	Corrected missing information	Section 9.2.4

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
description of exploratory biomarkers		
Revised text for amyloid CSF sampling to note that 2 methods are available rather than required	Revised for clarification	Section 9.5.1.3.3 Section 9.5.1.5 Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)
Specified definition of moderate or severe hepatic impairment	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Added that subjects who develop seizures will be discontinued from study drug.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3
Defined severe infection as follows: sepsis; deep tissue (invasive) infection; any infection requiring intravenous (IV) antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Added that for subjects who develop severe infections, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Revised study drug interruption and discontinuation criteria for skin rash and herpes infections. Added instructions for drug consultation with the Medical Monitor and potential rechallenge.	Clarification based upon feedback from Health Authority(ies)	Section 9.3.3 Section 9.5.1.5.1
Revidsed dose selection to note that PK/PD modeling indicates elenbecestat (E2609) 50 mg per day results in reduction of median CSF Aβ by approximately70%.	Clarification based upon feedback from Health Authority(ies)	Section 9.4.4
Corrected the description for calculating the immediate memory score on the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog_{14})	Corrected error	Section 9.5.1.3.1
Added measurement of prothrombin time, international normalized ratio (INR; derived from prothrombin time), and activated partial thromboplastin time (aPTT) to each study visit.	Added to support evaluation of hepatic function at each visit	Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)
Added clarification of the clinical assessment of suicidal thinking and behavior to be conducted at visits that do not include administration of the Columbia Suicide Severity Rating Scale (C-SSRS); which includes asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and asking their study partner "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?".	Clarification based upon feedback from Health Authority(ies)	Section 9.5.1.5.9

Revisions to Version 2.0

New version/date: Version 3.0/04 April 2017 (per Amendment 02)

Change	Rationale	Affected Protocol Sections
Corrected number of time points and blood volume per collection for assessments; added clarification that the volumes are estimates and my vary based on local regulations.	Corrected error	Section 9.5.2.2 and Table 4
Grammatical, typographical, and formatting changes were also made	Document quality	Throughout

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK in subjects with mild liver	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 2

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 2), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have prothrombin time and INR	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor subjects on anticoagulation/	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
(derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 3
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed from 8 to 9. A brief study	Results of the special population hepatic impairment study (E2609-	Section 7.1

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	A001-103) with elenbecestat (E2609) have become available.	
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 2, and Table 3)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2, and Table 3)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the QOL-AD …".	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 3)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 4)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 01)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01) V3.0 04 Apr 2017 (Amendment 02)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor

task. Subjects will also be evaluated on the modified Hachinski scale.

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory, PD (Aβ(1-x) and other isoforms), biomarker testing, and pharmacogenomics (PGx) analyses of *ApoE* genotype. (revised per Amendment 01) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects

who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 01)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an acetylcholinesterase inhibitor (AChEI) or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral

steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.

8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:

   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)
2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely

to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
    - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
    - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
    - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendment 01)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment

with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)
13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 01)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02) . Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to

cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Blood will be collected to measure plasma PD (Aβ1-x) at Screening and various timepoints during treatment and followup. (revised per Amendments 01 and 02)

Blood samples will be obtained at Screening and will be usedfor exploratory biomarker assessment and to determine the *ApoE* genotype of all subjects enrolled in this study . (revised per Amendments 01 and 02)

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug). PD and exploratory biomarker assessments will be performed on CSF collected from the substudy baseline and 24 month/ED assessment. (revised per Amendment 02)

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per

Amendment 02)

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner)

and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods. Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 01)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months

- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound

Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization

stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a

validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha = 0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form

Abbreviation	Term
CRO	contract research organization
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio

Abbreviation	Term
IRB	Institutional Review Board
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula

Abbreviation	Term
R	randomization
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment

crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 01)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat (E2609), tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the

lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5

metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

Preliminary PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609)is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609)is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild

AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

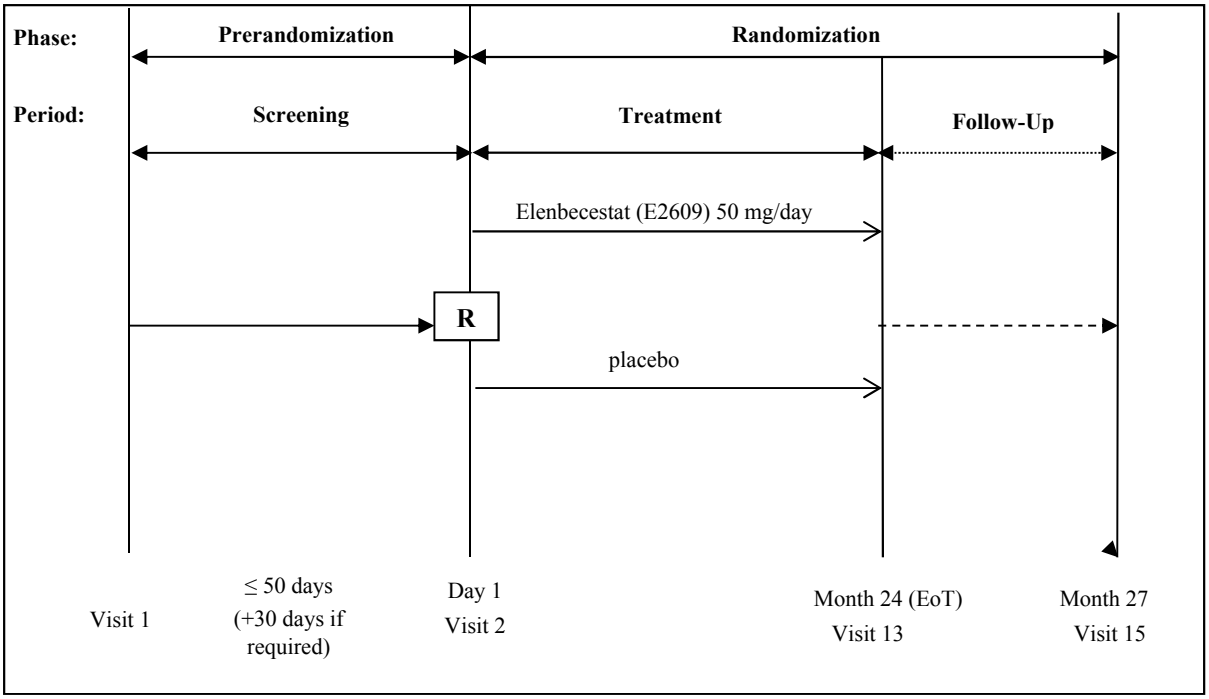

Figure 1 Study Design for E2609-G000-302

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF

substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarkers, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for testing as needed. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The start of the open-label Extension Phase will require prior approval of an amendment from applicable Health Authorities and will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. (revised per Amendment 02) Full details of the Extension Phase will be available in a future protocol amendment.

9.1.4 End of Study

The end of the study for the double-blind Randomization Phase will be the date of the last study visit (Visit 15) for the last subject in the double-blind Randomization Phase. (revised per Amendment 02)

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the

CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by elenbecestat (E2609) increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD

progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable

(Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and

subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects.

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma and CSF may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendments 01 and 02)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must

agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single

significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat (E2609)
- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects who develop moderate or severe hepatic impairment (eg, Child-Pugh Class B or C) during the study must discontinue study drug. (revised per Amendments 01 and 02) Moderate or severe hepatic impairment are defined as any 2 of the following criteria: INR ≥ 1.7; bilirubin ≥ 1.5 × ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 02)

Subjects who develop seizures will be discontinued from study drug. (revised per Amendment 02)

In the event that a subject develops a severe infection, study drug administration should be interrupted for a maximum period of 4 weeks. Examples of severe infections include the following: sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis. Subjects who recover from severe infections within 4 weeks may resume treatment if deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the severe infection has not resolved within 4 weeks. (revised per Amendment 02)

As described under Dermatologic Assessment in Section 9.5.1.5.5, in the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered “on study” as long as they continue to return for their regularly

scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by

manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on the PK/PD modeling results, elenbecestat (E2609) 50 mg per day reduced median CSF Aβ by approximately 70%. (revised per Amendment 02) Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 01)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.
d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should be undertaken in compliance with local standard of care for symptomatic treatment of AD. (revised per Amendment 02). Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with the Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to:

(a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus

(chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word Recall and Delayed Word Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For Word Recall, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the average number of words incorrectly recalled during 3 trials. Word Recall is administered near the beginning of the ADAS-Cog$_{14}$. A few minutes later, the subject is asked to recall as many words as possible from the previously studied list. The total number of words incorrectly recalled on this Delayed Word Recall task ranges from 0-10. (revised per Amendment 02)

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake.

Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods available at screening to determine subject eligibility for the study. (revised per Amendment 02 Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609).

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed.

Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK blood sample will be collected either shortly before or shortly after the LP. (revised per Amendment 02)

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Biomarkers

The CSF sample will be used for PD and exploratory assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity. . (revised per Amendment 02)

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 activity levels will be measured using internally developed fluorescence resonance energy transfer and BACE protein levels will be measured using ELISA based assay(s). (revised per Amendment 02) Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD/exploratory biomarker assessments as specified in Table 2 and Table 3. (revised per Amendment 02) The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples for immunologic assessments and CSF (if applicable) collected at Screening will also be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). (revised per Amendment 02) Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for

immunologic assessments will be collected as outlined in Table 2 and Table 3. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing as required. (revised per Amendment 02) The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated

suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection (eg, sepsis; deep tissue (invasive) infection; any infection requiring IV antibiotics; any infection requiring hospitalization (if outpatient at onset); any infection leading to need for oxygen, pressors or fluids to support blood pressure, or intubation; any infection that requires major surgical intervention; pseudomembranous colitis due to *C. difficile*; typhlitis; osteomyelitis; and meningitis); any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality. (revised per Amendment 02)

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils), rothrombin time, INR (derived from prothrombin time) and aPTT are to be performed for all subjects as part of Screening and at each visit (revised per Amendments 01 and 02). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing as required. (revised per Amendment 02) Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

aPTT = activated partial thromboplastin time, CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

In the event that a subject develops any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), study drug administration should be interrupted for a maximum period of 4 weeks and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. (revised per Amendment 02) For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity. Subjects who recover from skin rash within 4 weeks may resume treatment if in the opinion of the dermatologic consult, the rash was not drug related and it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the skin rash has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

In the event that a subject develops moderate to severe oral or genital herpes, study drug administration should be interrupted for a maximum period of 4 weeks. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours. Subjects who recover from moderate to severe oral or genital herpes within 4 weeks may resume treatment if it is deemed appropriate by the investigator after consultation with the Medical Monitor. Subjects should permanently discontinue study drug if the oral or genital herpes has not resolved within 4 weeks or returns during rechallenge. (revised per Amendment 02)

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. At visits that the the C-SSRS is not administered, the clinical assessment of suicidality will include asking the subject "Since the last time we spoke have you had any thoughts or attempts to end your life by suicide?" and their study partner will be asked "Since the last time we spoke has the subject shared any thoughts or are you aware of attempts at suicide?". (revised per Amendment 02) A positive suicidality assessment from the subject or their study partner on the clinical assessment of suicidality will trigger the C-SSRS to be administered. (revised per Amendment 032) A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, coagulation, thyroid function, vitamin B12[h] (revised per Amendmemnt 02)	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and other biomarkers[j]	X (Tier 3)

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Blood sample for immunologic assessments, including isolation of PBMCs for storage and testing as required (revised per Amendment 02)	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD/exploratory biomarker baseline)[n,o,p] (revised per Amendment 02)	X (Tier 5)

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study).

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time, INR derived from the prothrombin time, and aPTT are to be performed as part of Screening (revised per Amendments 01 and 02).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD/exploratory biomarker baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP. (revised per Amendment 02)

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

l: Only required for female subjects of child-bearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry, hematology, and coagulation (reviser per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and testing as required (reviser per Amendment 02)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and other biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[x]												X	X			

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if

no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, 13 (or ED), 14, and 15. ((revised per Amendment 02)

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that might indicate signals of possible drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire); categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3. (revised per Amendments 01)

[aa] The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the estimated total volume of blood and CSF that will be collected throughout the study. (revised per Amendment 02) Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety. Actual specimen volumes may vary based on local regulations. (revised per Amendment 02)

Table 4 Summary of Estimated Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points × Volume per Collection (mL)		Total Volume[a] (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry (revised per Amendment 02)	15	1×2.5 mL	14×2.5 mL	37.5 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Coagulation (revised per Amendment 02)	15	1×1.8 mL	14×1.8 mL	27 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	none	5 mL
Viral screen at Screening (Hepatitis B and C) (revised per Amendment 02)	1	1×2.5 mL	none	2.5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.) (revised per Amendment 02)	1	none	1×3.5 mL	3.5 mL
Vitamin B12 at Screening (revised per Amendment 02)	1	can use blood drawn for TFT	none	no additional volume
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing	15	1×20 mL	14×20 mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample (revised per Amendments 01 and 02)	10	1×24 mL	9×6 mL	78 mL
PK analysis (revised per Amendment 02)	7	none	14×2 mL	28 mL
Pharmacogenomic sample (revised per Amendments 01 and 02)	1	1×6 mL	none	6 mL
All blood samples, total volume collected (revised per Amendments 01 and 02)		61.3 mL	458.7 mL	520 mL
CSF				
Amyloid eligibility	1	1×12 mL	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic, TFT = thyroid function Test.

a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit) ; actual volume may vary based on local regulations. (revised per Amendment 02)

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their

last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is

planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is

significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of

treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category

will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs

will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and . Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic or Ocular Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendment 01)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Excessive happiness
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Psychotic episode or disorder
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors:

PPD

Eisai Ltd.

Date

PPD

Eisai, Inc.

Date

PPD

Eisai Inc.

Date

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

REVISION HISTORY

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
An editorial revision was made to add "elenbecestat", the proposed International Nonproprietary Name (pINN) for "E2609"; grammatical, typographical, and formatting changes were also made	The revision was made to provide consistency for current and future elenbecestat (E2609) clinical development documents.	All sections of the protocol that previously included "E2609" or required editorial revision
Revised the first exploratory objective to the following: To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate	To include exploration of the PD relationship of study drug to PK, efficacy, and immune function	Synopsis • Exploratory Objectives • Study Design • Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments • Bioanalytical Methods Section 8.3 Section 9.2.4
Added exclusion criterion for moderate to severe hepatic impairment: Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: international normalized ratio (INR) ≥ 1.7; bilirubin ≥ 1.5 × upper limit of normal (ULN); albumin < lower limit of normal (LLN); ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria	The revision was made in light of data from hepatic impairment Study E2609-A001-103, which indicated an average increase in plasma elenbecestat (E2609) maximum observed concentration (C_{max}) and area under the concentration × time curve (AUC) of approximately 91% and 45%, respectively, in patients with moderate liver impairment (Child-Pugh Class B). There were no clinically meaningful effects on elenbecestat (E2609) PK	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 2

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
for moderate impairment. In the table of clinical laboratory tests (Table 1) and Schedule of Procedures/ Assessment (Table 2), prothrombin time and INR (derived from prothrombin time) were added as a required part of Screening. Modified exclusion criterion for "Any other clinically significant abnormalities" to remove "severe hepatic impairment"	in subjects with mild liver impairment (Child-Pugh Class A) relative to control. Mandatory evaluation of prothrombin time and INR at Screening for all subjects was added for evaluation of potential hepatic impairment. The new exclusion criterion specifically added to exclude subjects with moderate or severe hepatic impairment made the exclusion of subjects with "severe hepatic impairment" redundant in the "Any other clinically significant abnormalities" criterion	
Added that subjects who developed moderate to severe hepatic impairment during the study must discontinue study drug.	To align with exclusion criterion for moderate to severe hepatic impairment, based on data from the hepatic impairment study (E2609-A001-103)	Section 9.3.3
Removed exclusion criterion for "Subjects who undergo cerebrospinal fluid (CSF) lumbar puncture (LP) procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) Additional guidance is provided for subjects receiving concomitant anticoagulation/ antiplatelet therapy; these subjects should have	Clarification that although subjects with bleeding risk (as judged by the investigator) may not undergo CSF LP, they are not excluded or discontinued from the main study if the bleeding risk is due to permitted concomitant anticoagulation/ antiplatelet therapy; the revision was made to provide guidance to the investigator to monitor	Synopsis • Exclusion Criteria Section 9.3.2 Section 9.5.1.3.3 Section 9.5.1.5.3 (Table 1) Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
prothrombin time and INR (derived from prothrombin time) prior to CSF LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection.	subjects on anticoagulation/ antiplatelet therapy regarding LP bleeding, based on the appropriate standard of care and the investigator's judgment	
Added clarification to the exclusion criteria for absolute lymphocyte count (ALC) that ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes.	Clarification to explain the standardized method of ALC calculation used across sites	Synopsis • Exclusion Criteria • Safety Assessments Section 9.3.2 Section 9.3.3 Section 9.5.1.5.1 Section 9.5.1.5.3, Table 1 Section 9.5.2.1, Table 3
The time frame restricting the concomitant drugs not permitted has been revised to specify "until the last visit during the treatment period" instead of "throughout the study"; "live/live attenuated vaccines" were added to the list of concomitant drugs not permitted Also added that concomitant therapy with acetylcholinesterase inhibitor (AChEI) or memantine should follow the local standard of care for symptomatic treatment.	Added for clarification	Synopsis • Concomitant Drug/Therapy Section 9.4.7 Appendix 2
The number of completed Phase 1 studies was changed	Results of the special population hepatic	Section 7.1

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
from 8 to 9. A brief study description and key results were added for the recently completed special population hepatic impairment study (E2609-A001-103) that indicated increased exposure of elenbecestat (E2609) for C_{max} and AUC pharmacokinetic (PK) parameters for subjects classified as Child-Pugh Class B or those with moderate hepatic impairment compared to age, sex, and body weight matched healthy controls.	impairment study (E2609-A001-103) with elenbecestat (E2609) have become available.	
Added that subjects who are assessed by both amyloid positron emission tomography (PET) and cerebrospinal fluid (CSF) are required to wait for a minimum of 48 hours between the 2 procedures and deleted that CSF must be collected before PET assessment	Time frame of 48 hours between PET tracer and CSF collections allow: a) wash out of PET tracer if CSF collection is done after PET, and b) subject clinical status is normalized prior to PET assessment if CSF was collected before.	Section 9.1.1.1 Section 9.1.1.1.5 Section 9.1.2 Section 9.1.2.1 Section 9.5.2.1 (Table 2, and Table 3)
Language to list the questionnaire for EuroQol - 5 Dimensions (EQ-5D) was changed from "There are 3 components to the EQ-5D…" to "There are 3 separate administrations of the EQ-5D…"	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2, and Table 3)
Language to list the questionnaire for Quality of Life in Alzheimer's Disease (QOL-AD) was changed from "There are 2 components to the QOL-AD …" to "There are 2 separate administrations of the	The language was revised for accuracy and clarification.	Section 9.1.1.1.2 and Section 9.5.2.1 (Table 2 and Table 3)

Revisions to Version 1.0

New version/date: Version 2.0/06 Feb 2017 (per Amendment 01)

Change	Rationale	Affected Protocol Sections
QOL-AD …".		
The bullet point describing the principal investigator's curriculum vitae requirement was updated as follows: "Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae)"	The revision was made to recognize that the principal investigator may not be a physician, but appropriate documentation of their qualification credentials must be provided with their curriculum vitae.	Section 9.4.9
Completion of the Sleep/Dream Questionnaire when triggered by AEs related to abnormal dreams, nightmares, or sleep terror was added for all study visits Completion of the Possible Drug Abuse Potential Form/ Questionnaire when subjects report AEs that might indicate signals of possible drug abuse potential was added for all study visits	The revision was made because the additional forms and questionnaires should be used if indicated, anytime a reported AE meets the qualification for the additional information.	Section 9.5.2.1 (Table 3)
Blood volumes for PK, pharmacodynamic (PD), and exploratory biomarkers were revised	Corrected to align with the Schedule of Procedures/ Assessments	Section 9.5.2.2 (Table 4)
Added the monoclonal antibody denosumab (Prolia) to the listing of prohibited immunoglobulin therapy and biologic drugs	Updated listing with currently available treatment	Appendix 2

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	Elenbecestat* (E2609) * the proposed International Nonproprietary Name (pINN) (revised per Amendment 01)
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol) V2.0 06 Feb 2017 (Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and

Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months
- To evaluate the population pharmacokinetics (PK) of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

The following health-related quality of life assessments will also be collected at the Screening Visit

and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory, PD (Aβ(1-x) and other isoforms), biomarker testing, and pharmacogenomics (PGx) analyses of *ApoE* genotype. (revised per Amendment 01) Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of child-bearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the procedures. (revised per Amendment 01) A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog_{14}, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, PD, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the Amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (revised per Amendment 01)

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of

treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study

partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)
2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:
    - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
    - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening
7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
    - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count $\times$ percentage of lymphocytes. (revised per Amendment 01)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - elenbecestat (E2609)
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 01)

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have

a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant/antiplatelet medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines. (revised per Amendment 01)

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of elenbecestat (E2609) concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Plasma will be collected to measure PD (Aβ1-x) at baseline and various timepoints during treatment and followup. (revised per Amendment 01)

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of all subjects enrolled in this study. (revised per Amendment 01)

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug).

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendment 02)

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every

6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods. Exploratory biomarkers such as neurofilament NFL, Ng, and VILIP1 may also be measured using validated assays. (revised per Amendment 01)

Plasma concentrations of elenbecestat (E2609) that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant biomarkers will be measured in the blood samples collected at times that match the PK draws and during the Followup Period. (revised per Amendment 01)

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI

- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months

Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from

baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization

stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a

validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
AST	aspartate aminotransferase
AUC	area under the concentration × time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	child-bearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization

Abbreviation	Term
CSF	cerebrospinal fluid
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board

Abbreviation	Term
ISLT	International Shopping List Task
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFL	neurofilament light
Ng	neurogranin
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
pINN	proposed International Nonproprietary Name
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization

Abbreviation	Term
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
VILIP1	visinin like protein 1
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

Elenbecestat (E2609) is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, elenbecestat (E2609) inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, elenbecestat (E2609) has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (Elenbecestat (E2609) Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of elenbecestat (E2609). Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 elenbecestat (E2609) program, and is primarily designed to evaluate the efficacy, safety, and tolerability of elenbecestat (E2609) in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of elenbecestat (E2609) has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by elenbecestat (E2609) in a clinical setting. Further details of the nonclinical data to date with elenbecestat (E2609) can be found in the Investigator's Brochure.

The clinical program to date includes 9 Phase 1 studies and 1 Phase 2 study: (revised per Amendment 01)

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of elenbecestat (E2609) and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of elenbecestat (E2609). It also investigated the effects of elenbecestat (E2609) on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of elenbecestat (E2609) on QTc interval in healthy subjects (thorough QT study). Two dose levels of elenbecestat (E2609) were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of elenbecestat (E2609) in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment

crossover study of single oral doses of a capsule formulation of elenbecestat (E2609) under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

Study E2609-A001-101 (Study 101) has been completed. This study was a Phase 1 randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults aged 50 to 85 years with subjective memory complaints and who qualified as having MCI or mild AD.

For Study E2609-A001-103 (Study 103), PK analysis has been completed and a clinical study report is in preparation. This study was a Phase 1 hepatic impairment special population study that enrolled 8 subjects with mild hepatic impairment (Child-Pugh Class A) and 8 subjects with moderate hepatic impairment (Child-Pugh Class B) and compared them to an equal number of age, sex, and body weight matched healthy control subjects following administration of a single oral 50 mg dose of elenbecestat (E2609). (revised per Amendment 01)

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with elenbecestat (E2609). The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with elenbecestat (E2609). In elderly subjects treated with 50 mg of elenbecestat (E2609), tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of elenbecestat (E2609) might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that elenbecestat (E2609) altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of elenbecestat (E2609). A single dose of elenbecestat (E2609) up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, elenbecestat (E2609) administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the

lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of elenbecestat (E2609) on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild increase (by approximately 70%) of the area under the concentration × time curve (AUC) of elenbecestat (E2609). Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of elenbecestat (E2609). Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of elenbecestat (E2609) when coadministered with elenbecestat (E2609) but not when dosed at least 2 hours apart from elenbecestat (E2609). Elenbecestat (E2609) (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of elenbecestat (E2609). Based on these results, it is not considered necessary to impose restrictions during elenbecestat (E2609) treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between elenbecestat (E2609) and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of elenbecestat (E2609) up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of elenbecestat (E2609). The effects of elenbecestat (E2609) on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg elenbecestat (E2609). This indicated that the M5

metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the elenbecestat (E2609) plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of elenbecestat (E2609) were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of TEAEs. There were no AEs of special interest or viral infections. There were no effects of elenbecestat (E2609) on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of elenbecestat (E2609) doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the elenbecestat (E2609) concentrations and QTcF effect was similar between Japanese and white subjects at the elenbecestat (E2609) dose of 50 mg.

Preliminary PK analysis of the data from Study 103 (hepatic impairment) showed that there was no clinically meaningful impact of mild hepatic impairment (Child-Pugh Class A) on the elenbecestat (E2609) PK parameters (C_{max} and AUC). However, in the subjects with moderate hepatic impairment (Child-Pugh Class B), average plasma elenbecestat (E2609) values for C_{max} and $AUC_{(0\text{-}inf)}$ following administration of a single 50 mg oral dose were approximately 91% and 45% higher, respectively, than healthy control subjects matched based on age, sex, and body weight Based on the finding of increased plasma concentrations of elenbecestat (E2609) in subjects with moderate hepatic impairment, the exclusion criteria for the study have been updated to exclude subjects with moderate to severe hepatic impairment. Subjects with mild hepatic impairment are eligible for study participation. (revised per Amendment 01)

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of elenbecestat (E2609) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether elenbecestat (E2609) is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months
- To evaluate the population PK of elenbecestat (E2609) in subjects with EAD

Biomarker Objectives

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609)is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609)is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the relationship between elenbecestat (E2609) exposure/PD (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) as deemed appropriate (revised per Amendment 01)
- To evaluate whether elenbecestat (E2609) is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether elenbecestat (E2609) is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether elenbecestat (E2609) is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether elenbecestat (E2609) is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al., 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al., 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of region are:

1. North America
2. Western Europe (including Oceania region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild

AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

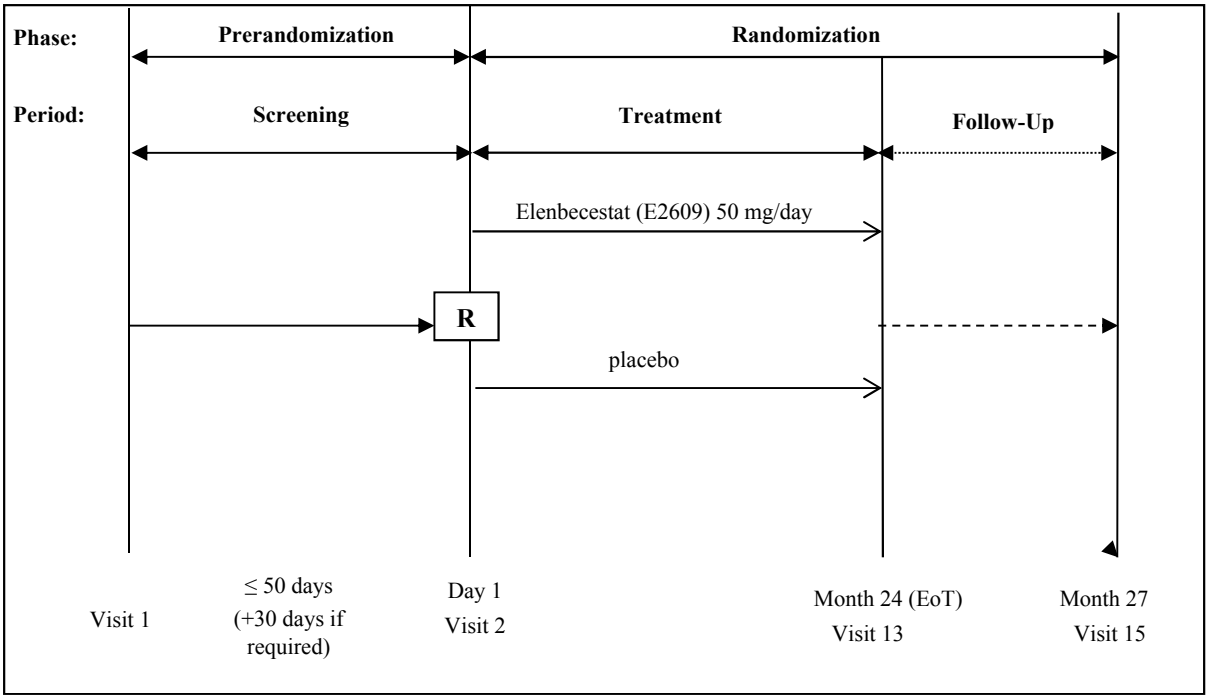

Figure 1 Study Design for E2609-G000-302

Elenbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF

substudy after Tier 5, ie during the Randomization Phase of the study. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 separate administrations of the EQ-5D as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 separate administrations of the QOL-AD as follows (revised per Amendment 01): (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarker assays, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). (revised per Amendment 01)

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child-bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cells (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat (E2609) 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Note that subjects who are assessed by both amyloid PET and CSF Aβ(1-42) are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01) Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day elenbecestat [E2609]) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of elenbecestat (E2609) compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score

using a standardized algorithm and a cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of elenbecestat (E2609) compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important biomarker endpoints will evaluate the AD modifying properties of elenbecestat (E2609) by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of elenbecestat (E2609) on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by elenbecestat (E2609) has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by elenbecestat (E2609) increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as elenbecestat (E2609). This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with elenbecestat (E2609) are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the

selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog_{14} immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with elenbecestat (E2609) treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether elenbecestat (E2609) is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether elenbecestat (E2609) is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether elenbecestat (E2609) is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the baseline imaging variables to help explain differences in treatment response between subjects.

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of elenbecestat (E2609) on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of elenbecestat (E2609) on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Exploratory Biomarkers

Exploratory biomarkers in plasma may be measured as validated assays (such as neurofilament light [NFL], neurogranin [Ng], or visinin like protein 1 [VILIP1]) become available. (revised per Amendment 01)

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.

7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of child-bearing potential who:
   - within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must

agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

NOTE: All females will be considered to be of child-bearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who have a history of moderate to severe hepatic impairment (eg, Child-Pugh Class B or C). Any 2 of the following criteria at Screening would exclude the subject: INR $\geq$ 1.7; bilirubin $\geq$ 1.5 $\times$ ULN; albumin < LLN; ascites or hepatic encephalopathy. Please note that a single

significant abnormality could meet criteria for moderate impairment. (revised per Amendment 01)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count (ALC) below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher); ALC will be derived from the complete blood count (CBC) with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

- Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

- Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments (revised per Amendment 01)

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

- elenbecestat (E2609)
- any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
- any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects who develop moderate or severe hepatic impairment during the study must discontinue study drug. (revised per Amendment 01)

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is elenbecestat (E2609) and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the elenbecestat (E2609) arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

Elenbecestat (E2609) will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match elenbecestat (E2609) will be of identical appearance. Each subject will receive 1 tablet of 50 mg elenbecestat (E2609) or an identical

placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for elenbecestat (E2609) and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either elenbecestat (E2609) or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of Elenbecestat (E2609)

- Test drug code: E2609
- Generic name: elenbecestat (pINN)
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

Elenbecestat (E2609) will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally

required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of elenbecestat (E2609) 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of elenbecestat (E2609) given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with elenbecestat (E2609) 5, 15, and 50 mg per day. Based on these results elenbecestat (E2609) 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) and this, in turn, should translate into greater clinical benefit while minimizing the safety concerns. Based on these data, elenbecestat (E2609) 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

Elenbecestat (E2609) is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

Elenbecestat (E2609) and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and

sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and until the last visit during the treatment period: (revised per Amendment 01)

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening and until the last visit during the treatment period (revised per Amendment 01)
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization and until the last visit during the treatment period (revised per Amendment 01)
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before

randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

d) Live/live attenuated vaccines are not permitted within 3 months before randomization and until the last treatment visit (this does not apply to non-live/inactivated vaccines) (revised per Amendment 01)

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted and should follow the local standard of care for symptomatic treatment (revised per Amendment 01). Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- Current medical license or proof of qualification of principal investigator (not required for sites outside North America if the qualification can be verified by their curriculum vitae) (revised per Amendment 01)
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word List Learning Immediate and Delayed Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989), (cited by Mohs et al., 1997). For this task, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the total number of words recalled during all 3 trials. The total number of words recalled ranges from 0-30. This task is given at the beginning of the ADAS-Cog$_{14}$. At the end of the ADAS-Cog$_{14}$, the subject is asked to recall as many words as possible from the previously studied list. The total number of words recalled on this Delayed Recall task ranges from 0-10.

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in

Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of elenbecestat (E2609) on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods required at screening to determine subject eligibility for the study. Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR results should be reviewed for subjects who consent to provide a CSF sample and are on concomitant anticoagulation/antiplatelet therapy, prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of elenbecestat (E2609) in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with elenbecestat (E2609).

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples

will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 Pharmacodynamic, Pharmacogenomic, and Other Biomarker, Assessments

Biomarkers

The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity.

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD assessments as specified in Table 2 and Table 3. The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples and CSF (if applicable) collected at Screening will be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in elenbecestat (E2609) exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 2 and Table 3. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

9.5.1.5.1 Adverse Events and Events Associated With Special Situations

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is elenbecestat (E2609).

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis

- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 Serious Adverse Events and Events Associated with Special Situations

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes[a], monocytes, neutrophils) Prothrombin time and INR (derived from prothrombin time) are to be performed for all subjects as part of Screening (revised per Amendment 01). A prothrombin time and INR should also be performed prior to LP for subjects who consent to provide a CSF sample later in the study (ie, postrandomization) and are on anticoagulation/antiplatelet therapy (revised per Amendment 01)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing. Cerebrospinal fluid sampling (see Hematology [above] for INR testing)

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMCs = peripheral blood mononuclear cells

a: ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or

infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of child-bearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of child-bearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive suicidality assessment on the clinical assessment of suicidality will trigger a C-SSRS to be administered. A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit.

Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, thyroid function, vitamin B12[h]	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and other biomarkers[j]	X (Tier 3)
Blood sample for immunologic assessments, including isolation of PBMCs for storage and later testing	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD baseline)[n,o,p]	X (Tier 5)

NOTES:

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study).

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

e: There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner (revised per Amendment 01)

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine. Prothrombin time and INR derived from the prothrombin time are to be performed as part of Screening (revised per Amendment 01).

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP.

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of child-bearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. Subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures (revised per Amendment 01). A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, the 2 assessments should be separated by at least 48 hours between the 2 procedures. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. (revised per Amendment 01)

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and later testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and other biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[x]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Sleep/Dream Questionnaire[y]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Possible Drug Abuse Potential Form/ Questionnaire[z]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Randomization	X															
Dispense study drug	X[aa]	X	X	X	X	X	X	X	X	X	X					

Notes

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = child-bearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have ALC measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. ALC will be derived from the CBC with differential representing the normal lymphocytes (with atypical lymphocytes removed and presented as a separate count if they are present) and calculated by the white blood cell count × percentage of lymphocytes. (revised per Amendment 01)

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

[o] Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

[p] The clinical assessment of suicidality will require input from both the subject and the study partner

[q] There are 3 separate administrations of the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner (revised per Amendment 01)

[r] There are 2 separate administrations of the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner (revised per Amendment 01)

[s] MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

[t] PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

[u] Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood

sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

[v] Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

[w] PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED).

[x] For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects receiving concomitant anticoagulation/antiplatelet therapy should have prothrombin time and INR (derived from prothrombin time) prior to LP; if they are assessed by the investigator to be at risk for bleeding, they are to be excluded from CSF collection. Note that subjects who are assessed by both amyloid PET and CSF are required to wait for a minimum of 48 hours between the 2 procedures. (revised per Amendment 01)

[y] Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

[z] AEs that might indicate signals of possible drug abuse potential require a more detailed follow-up through completion of a specific eCRF form (Possible drug abuse potential form/ questionnaire); categories and examples of AEs indicating signals of possible drug abuse are provided in Appendix 3. (revised per Amendments 01)

[aa] The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

Table 4 Summary of Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points x Volume per Collection (mL)		Total Volume[a] (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry	15	1×5 mL	14×5 mL	75 mL
Serum pregnancy test at Screening (females of child-bearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	None	5 mL
Viral screen at Screening (Hepatitis B and C)	1	1×5 mL	None	5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.)	1	None	1 x 4 mL	4 mL
Vitamin B12 at Screening	1	1×5mL	None	5 mL
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing	15	1×20 mL	14×20mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample (revised per Amendment 01)	10	1×24 mL	9×12 mL	132 mL
PK analysis	7	none	7×4 mL	28 mL
Pharmacogenomic sample (revised per Amendment 01)	1	1×3 mL	None	3 mL
All blood samples, total volume collected (revised per Amendment 01)		69 mL	558 mL	627 mL
CSF				
Amyloid eligibility	1	1×12 mL	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMCs = peripheral blood mononuclear cells, PD = pharmacodynamics, PK = pharmacokinetic.

a: The total volume includes all blood/CSF collection from Screening through Week 117 (Followup Visit).

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their

last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is

planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months

- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable elenbecestat (E2609) plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for

screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare elenbecestat (E2609) 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for elenbecestat (E2609) versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between elenbecestat (E2609) 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for elenbecestat (E2609) 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha = 0.05, ie, any test will start only if the test with higher hierarchical order is

significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of

treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual elenbecestat (E2609) plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of elenbecestat (E2609) plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of elenbecestat (E2609). The effect of covariates (ie, demographics) on elenbecestat (E2609) PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of elenbecestat (E2609) will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of elenbecestat (E2609) with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat (E2609) and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat (E2609) and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to elenbecestat (E2609) and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare elenbecestat (E2609) versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category

will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs

will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog$_{14}$, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of elenbecestat (E2609) versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the elenbecestat (E2609) 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between elenbecestat (E2609) 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low	<LLN – 2.5 mg/dL	<2.5 – 2.0 mg/dL	<2.0 – 1.0 mg/dL	<1.0 mg/dL

	Grade 1	Grade 2	Grade 3	Grade 4
(hypophosphatemia)	<LLN – 0.8 mmol/L	<0.8 – 0.6 mmol/L	<0.6 – 0.3 mmol/L	<0.3 mmol/L life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and . Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization and Until the Last Visit During the Treatment Period

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline and Until the Last Visit During the Treatment Period

Systemic or Ocular Immunosuppressants[a] and Immunomodulatory Drugs (revised per Amendment 01)	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral

Prohibited Medications Within 6 Months Before Screening and Until the Last Visit During the Treatment Period (revised per Amendment 01)

Immunoglobulin Therapy and Biologic Drugs (revised per Amendment 01)	
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Denosumab	Prolia (revised per Amendment 01)
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization and Until the Last Visit During the Treatment Period (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Excessive happiness
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
		Psychotic episode or disorder
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

SIGNATURES

Authors:

PPD

Date

Eisai Ltd.

PPD

Date

Eisai, Inc.

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	Elenbecestat* (E2609) * pINN (revised per Amendment 01)
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date

1 TITLE PAGE

Clinical Study Protocol

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Ltd. European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK Eisai Co., Ltd. 4-6-10 Koishikawa Bunkyo-Ku, Tokyo 112 8088 Japan
Investigational Product Name:	E2609
Indication:	Alzheimer's disease
Phase:	3
Approval Date:	V1.0 16 Nov 2016 (original protocol)
IND Number:	109308
EudraCT Number:	2016-004128-42
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 CLINICAL PROTOCOL SYNOPSIS

Compound No.: E2609

Name of Active Ingredient: *N*-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide

Study Protocol Title

A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigator(s)

Unknown

Site(s)

Up to approximately 350 global sites

Study Period and Phase of Development

- The study period for an individual subject is 29 months, including 2 months of screening, 24 months of treatment, and 3 months of posttreatment follow-up in the core study period. An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core Study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.
- Phase 3

Objectives

Primary Objective

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with Early Alzheimer's Disease (EAD)

Secondary Objectives

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of Clinical Dementia Rating (CDR) scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD

- To determine whether E2609 is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], functional MRI [fMRI]) at 24 months
- To evaluate the population pharmacokinetics (PK) of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid positron emission tomography (PET) in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease (AD) as deemed appropriate

Exploratory Objectives

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

Study Design

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including mild cognitive impairment (MCI) due to AD/Prodromal AD and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial

availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging (with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD), and concurrent AD medication use. The 7 levels of the region are:

1. North America
2. Western Europe (including Oceana region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

Conduct of the Core Study

The Core Study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). The following cognitive assessments will be conducted at Screening: MMSE, International Shopping List Task (ISLT), and CDR. The ISLT total recall and delayed recall are to be administered with the Cogstate Brief Battery (CBB) in between as a distractor task. Subjects will also be evaluated on the modified Hachinski scale.

The following health-related quality of life assessments will also be collected at the Screening Visit and will provide baseline values for the study: EQ-5D (administered to both the subject and the study partner), QOL-AD (administered to both the subject and the study partner), and the Zarit's Burden Interview. The study partner needs to be available either in person or via telephone for these assessments.

Subjects will also be evaluated on the Columbia Suicide Severity Rating Scale (C-SSRS) for

eligibility.

Following these initial assessments, blood will be collected from all subjects for clinical laboratory and biomarker testing and pharmacogenomics (PGx) analyses of *ApoE* genotype. Vital signs and weight will be recorded, and a single 12-lead electrocardiogram (ECG) will be conducted. A complete physical examination with dermatologic review and a full neurologic exam will be conducted. Additionally, a serum pregnancy test for females of childbearing potential will be performed.

Subjects who pass the initial clinical and safety screen for eligibility will be then assessed via magnetic resonance imaging (MRI) for brain abnormalities which may exclude study participation. An additional scanning sequence for vMRI assessment, along with sequences for task free resting fMRI, will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

For further assessment of eligibility, subjects who have met all eligibility criteria thus far will then be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or CSF Aβ(1-42), the Aβ monomer from amino acid 1 to 42 (Screening CSF) or both. For those subjects who initially consent to both CSF and PET eligibility assessments, the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. A positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other positive result).

The Screening amyloid PET and/or Screening CSF will serve as the baseline data for subjects in the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies.

Eligible subjects will proceed into the Randomization Phase.

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. During Visit 2, the subject will complete additional baseline assessments before receiving the first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of adverse events (AEs). A single 12-lead ECG will be conducted. The C-SSRS will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing, urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken and stored.

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, MRI, and vMRI (including sequences for fMRI), while those subjects who consent to participate in the amyloid PET and/or CSF substudy will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol.

The CDR will be conducted every 3 months during the Core Study; other cognitive assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of disease (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be

undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the Early Discontinuation (ED)/Follow-Up visit.

In some cases, unscheduled (UNS) visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment (or at the ED visit, provided the subject has received at least 39 weeks of study drug).

Safety assessments including physical examinations with dermatologic review by the study investigator, neurologic exams, assessments of suicidal thinking and behavior, standard laboratory assessments, centrally-read ECGs, and blood assessment for PK will be performed throughout the 24 months of treatment in the study. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment during the Core Study will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

Data Safety Monitoring Board

An independent Data Safety Monitoring Board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

Number of Subjects

Approximately 1330 subjects will be randomized into the study.

Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study

1. MCI due to Alzheimer's disease or Mild Alzheimer's disease according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
    a. MMSE score equal to or greater than 24
    b. CDR global score of 0.5
    c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
    a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for lumbar puncture (LP) to obtain CSF for testing of eligibility.
    b. CSF assessment of Aβ(1-42)

    NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be satisfied that the subject can contact the study partner

readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - total abstinence (if it is their preferred and usual lifestyle)
     - an intrauterine device or intrauterine hormone-releasing system
     - an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - have a vasectomized partner with confirmed azoospermia.
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)
2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD
3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening
4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening
5. Modified Hachinski Ischemia Score greater than 4 at Screening
6. Any of the following psychiatric symptoms:
   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures
   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been

hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or
    - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.
    - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).
8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3)
9. Results of laboratory tests conducted during screening that are outside the following limits:
    - Absolute lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher)
    - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)
    - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)
10. Subjects at risk of increased risk of infection, specifically:
    - Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection
    - Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve
    - Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin (Ig) deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)
11. Have received any live/live attenuated vaccine in the 3 months before randomization
12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:
    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.
    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.
    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:
    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.
    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments
    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately
14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.
15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.
16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary
17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening
18. Taking prohibited medications
19. Have participated in a clinical study involving:
    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug
    - E2609
    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo
    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization
20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

Study Treatments

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food.

Duration of Treatment

All subjects will receive 24 months of treatment in the study.

Concomitant Drug/Therapy

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening

b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization

c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Assessments

Efficacy Assessments

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

Pharmacokinetic Assessments

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. For subjects who consent to CSF sample collection, CSF samples will also be collected for the determination of E2609 concentrations.

Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

Amyloid PET imaging or CSF Aβ(1-42) assessment or both will be used to confirm that all study subjects have amyloid deposition in the brain. This criterion will confirm amyloid pathology and allow for the inclusion only of subjects with MCI due to AD/Mild AD. Use of a historical amyloid PET (conducted within 12 months before the planned randomization date) is acceptable for determination of eligibility (providing that the historical imaging data is made available to the sponsor) but will not suffice for baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy.

Subjects who consent to participate in the longitudinal amyloid PET or CSF or both substudies will also receive amyloid PET or CSF assessment or both at 12 months (PET only), 24 months, or at the ED visit (provided the subject has received at least 39 weeks of study drug).

T-tau and p-tau in the CSF are sensitive markers of axonal and neuronal degeneration (t-tau) and neurofibrillary tangles ([NFTs]; p-tau), and have been demonstrated to increase in parallel with disease progression.

All subjects will have *ApoE* genotyping performed.

Safety Assessments

Safety will be assessed by monitoring and recording all AEs and serious adverse events (SAEs); regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs; ECG recordings evaluated by a central reader; physical, dermatologic, and neurologic examinations; assessment of suicidality; and MRIs during the Treatment Period.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than 800/mm^3), this should be confirmed as soon as possible, but not later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a second occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects will be monitored for hypersensitivity reactions and infections by AEs, physical examinations with dermatologic review, and laboratory tests.

Dermatologic review will be conducted as part of the physical examination. These assessments will specifically include evaluation of any areas of depigmentation or drug-induced vitiligo as well as any evidence of rash. Subjects will also be questioned by the investigator at each visit to identify any changes that might represent a drug-induced rash/reaction or infection. Subjects and their study

partners will be instructed to contact the investigator if they see any lesions or other symptoms that might be associated with a drug-induced rash/reaction or infection, so that such AEs can be reviewed promptly. CBCs and percentages will be measured (by a centralized laboratory) every 2 weeks for the first month, and then monthly for the next 2 months (ie, until month 3 of treatment). Thereafter, they will be monitored every 3 months until the end of the Treatment Period and at both Follow-Up Visits.

An assessment of suicidality using the C-SSRS or a clinical assessment of suicidality will be performed at every visit.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up.

Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL in addition to the study partner's own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months.

Bioanalytical Methods

CSF levels of Aβ isoforms (eg, Aβ [1-42]) will be assessed for eligibility and treatment response in consenting subjects using validated, commercially available kits. CSF will also be analyzed for t-tau, p-tau and potentially Beta-Amyloid Converting Enzyme 1 (BACE1) enzyme levels and activity in all collected samples using validated methods.

Plasma concentrations of E2609 that may extend to the key metabolites M1, M2, and M5 will be measured by a validated assay using liquid chromatography method using tandem mass spectrometry.

Aβ(1-x) and other relevant PD biomarkers will be measured in the blood samples collected at times that match the PK draws.

Statistical Methods

All statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding.

Study Endpoints

Primary Endpoint

- Change from baseline in the CDR-SB at 24 months

Secondary Endpoints

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

Biomarker Endpoints

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

Exploratory Endpoints

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently complied with the protocol.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

Analyses for Primary Efficacy Endpoints

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using analysis of covariance model (ANCOVA) after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group, and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

Analyses for Secondary Efficacy Endpoints

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by

the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan–Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog14, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI,) at 24 months will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline values for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

Analyses for Biomarkers Endpoints

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, ANCOVA, etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with

the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

Analyses for Exploratory Efficacy Endpoints

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

Pharmacokinetics

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as area under the concentration × time curve (AUC) will be calculated from the model using the individual posterior estimate of CL and dosing history.

Pharmacokinetic-Pharmacodynamic

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration (C_{max}), and $AUC_{(0-24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the

MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

Other Analyses

MRI (including vMRI and fMRI) sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Interim Analyses

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

Sample Size Rationale

The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
Aβ	amyloid beta
Aβ(1-x)	amyloid beta (1-x) (ie, the amyloid beta monomer from amino acid 1 to x [eg 1-42])
AChEI	acetylcholinesterase inhibitor
AD	Alzheimer's disease
ADAS-cog	Alzheimer's Disease Assessment Scale - cognitive subscale
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
APP	amyloid precursor protein
AST	aspartate aminotransferase
AUC	area under the concentration x time curve
BACE1	beta-amyloid converting enzyme 1
BP	blood pressure
bpm	beats per minute
CBB	Cogstate Brief Battery
CBC	complete blood count
CBP	childbearing potential
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating -Sum Of Boxes
CES2	carboxylesterase-2
CFR	Code of Federal Regulations
C_{max}	maximum observed concentration
CI	confidence interval
CNS	central nervous system
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CSF	cerebrospinal fluid

Abbreviation	Term
C-SSRS	Columbia Suicide Severity Rating Scale
CTA	Clinical Trial Agreement
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DSMB	data safety monitoring board
ECG	electrocardiogram
eCRF	electronic case report form
EAD	Early Alzheimer's Disease.
ED	early discontinuation
ELISA	enzyme-linked immunosorbent assay
EQ-5D	EuroQol - 5 Dimensions
FAQ	Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire)
FAS	Full Analysis Set
FDA	Food and Drug Administration
fMRI	functional magnetic resonance imaging
GCP	Good Clinical Practice
GGT	γ-glutamyl transpeptidase
HBsAg	hepatitis B surface antigen
HCVAb	hepatitis C virus antibody
HRQoL	health related quality of life
HSV	herpes simplex virus
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ID	identifier
IEC	Independent Ethics Committee
Ig	immunoglobulin (eg, IgA, IgG, IgM)
INR	International Normalized Ratio
IRB	Institutional Review Board
ISLT	International Shopping List Task

Abbreviation	Term
IxRS	interactive voice and web response system
LME	linear mixed effects
LLN	lower limit of normal
LNH	low/normal/high
LP	lumbar puncture
MAD	multiple ascending dose
MCI	mild cognitive impairment
MedDRA	Medical Dictionary for Regulatory Activities
mild AD	mild dementia due to Alzheimer's Disease
MMRM	mixed effects model for repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
N/A	not applicable
NIA-AA	National Institute of Aging-Alzheimer's Association
NFTs	neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PBMC	peripheral blood mononuclear cell
PD	pharmacodynamic(s)
PET	positron emission tomography
PGx	pharmacogenomic(s)
PK	pharmacokinetic(s)
PPS	per protocol analysis set
PRN	pro re nata
PT	preferred term
p-tau	phosphorylated-tau
QD	once daily
QOL-AD	Quality of Life in Alzheimer's Disease
QTc	corrected QT interval
QTcF	QTc interval calculated using Fridericia's formula
R	randomization
SAD	single ascending dose
SAE	serious adverse event
SOC	system organ class
SUSAR	suspected unexpected serious adverse reaction

Abbreviation	Term
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIA	transient ischemic attacks
t-tau	total tau
ULN	upper limit of normal
UNS	unscheduled
vMRI	volumetric magnetic resonance imaging
WBC	white blood cell (count)
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 Institutional Review Boards/Independent Ethics Committees

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice[GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associate [CRA], change of telephone number). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC chairman must be sent to the principal investigator (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 Ethical Conduct of the Study

This study will be conducted in accordance with standard operating procedures of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2013.
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, ICH of Pharmaceuticals for Human Use.

- Title 21 of the United States Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any EU country. All SUSARs will be reported, as required, to the Competent Authorities of all involved EU member states.
- Article 14, Paragraph 3, and Article 80-2 of the Pharmaceutical Affairs Law (Law No. 145, 1960) for studies conducted in Japan, in addition to Japan's GCP
- Other applicable regulatory authorities' requirements or directives

5.3 Subject Information and Informed Consent

As part of administering the informed consent document, the investigator, or designee, must explain to each subject, the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedure(s) or course(s) of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to the subject's participation in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. The subject will be asked to sign an ICF at the Screening Visit before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

The identified study partner should also consent to supporting the subject's participation in the study and will be provided with a written ICF for his or her participation as a study partner in the study, to be signed before the Screening Visit Clinical Dementia Rating (CDR) is performed. The study partner need not consent on the same day as the subject.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject and identified study partner must sign an approved ICF before study participation. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject and identified study partner will be verified by the sponsor and kept on file according to local procedures at the site. The subject and the identified study partner should be informed in a timely manner if new information becomes available that may be relevant to the subject's and/or the study

partner's willingness to continue participation in the study. The communication of this information should be documented.

Subjects that agree to take part in the cerebrospinal fluid (CSF) and/or positron emission tomography (PET) longitudinal substudy will also be asked to provide separate written consent for these procedures.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at up to approximately 350 investigational sites globally.

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organization(s) (CRO[s]) are listed in the Investigator Study File or the Regulatory Binder provided to each site.

7 INTRODUCTION

Alzheimer's disease (AD) is the main cause of dementia and it is estimated that the condition affects around 40 million people worldwide, mostly older than 60 years (Prince, et al., 2013). Typical clinical signs and symptoms of AD include memory impairment and executive dysfunction progressively interfering more severely with daily life activities. The clinical diagnosis of any dementia including AD relies on accurate medical history from the patient and their caregivers, neuropsychological testing, and assessment of symptoms over time. However, during recent years, the advent of magnetic resonance imaging (MRI) and the discovery of CSF biomarkers and amyloid PET have contributed to a refinement of the diagnostic criteria for AD. New criteria proposed by the International Working Group (IWG), (Dubois, et al., 2014) set up the basis for the subsequent set of criteria by the National Institute of Aging and Alzheimer's Association (NIA–AA) working group. Critically, a relatively long pre-dementia stage is acknowledged in these criteria. While the term Prodromal AD is used for the pre-dementia stage criteria of the IWG, the NIA–AA criteria recognizes mild cognitive impairment (MCI) due to AD when supported by biomarkers suggesting the presence of amyloid and neurodegeneration (McKhann, et al., 2011; Albert, et al., 2011). Biomarker evidence can be used to attribute the clinical syndrome of dementia or MCI to underlying Alzheimer's pathological changes with high, intermediate, or low likelihood (ie, the likelihood that the diagnosis is AD) in the NIA–AA criteria.

The pathophysiology of AD is linked with the substantial evidence that accumulation of abnormally folded amyloid beta (Aβ) and tau proteins in amyloid plaques and neuronal tangles are causally related to neurodegenerative processes in the brain of subjects affected by AD (Lewczuk, et al., 2015; McKhann, et al., 2011; Muresan and Ladescu Muresan, 2015).

During recent years, an Aβ cascade hypothesis has been postulated to explain the pathological processes observed in the AD brain. In order to understand the Aβ cascade hypothesis, it is important to briefly review the functional biology of the Aβ protein and of its precursor protein. The amyloid precursor protein (APP) is a highly conserved, integral membrane protein whose expression is mainly localized around the synapse of neuronal tissue. While its primary role is not fully understood, it is postulated that its function may be related to neuronal plasticity and synapse formation (Zheng and Koo, 2006). The primary proteolytic events on APP and the pro- or anti-amyloid subsequent events occur at or around its transmembrane region by a group of secretase enzymes (α, β, and γ).

Two metabolic pathways (a non-amyloidogenic route and an amyloidogenic route) of APP occur physiologically in a healthy, normal brain. In brief, the anti-amyloidogenic or non-amyloidogenic process is initiated by α and γ- secretases and, in essence, this metabolic route produces non-aggregating, non-amyloidogenic proteins.

The alternate APP metabolic pathway is initiated via β-secretase or beta-amyloid converting enzyme 1 (BACE1) but is still concluded by γ-secretase. This β/γ-secretase pathway is referred to as the amyloidogenic metabolism of APP, as the release of the toxic Aβ-peptides (Aβ40 and Aβ42) is a consequence of the 2-step proteolytic process. It is noteworthy that

both APP metabolic pathways are part of normal physiology and that healthy brains have effective post-APP processing mechanisms to handle these by-products (Sambamurti, et al., 2002). It is hypothesized that in AD, APP functionality deviates from the norm as a wide range of regulatory mechanisms begin to fail – for example, APP metabolism shifts from primarily non-amyloidogenic to primarily amyloidogenic and/or there is an increased inefficiency in the clearance of liberated APP Aβ (Zhang, et al., 2011). The outcome during the early stages of AD is a rapid increase in the Aβ load; that increase in concentration drives the observed proteopathy in AD.

If the amyloid hypothesis is correct, inhibition of cerebral Aβ accumulation by inhibitors of BACE1 could benefit patients with AD by potentially lowering cerebral Aβ concentrations and thereby slowing the progression of cognitive decline. Unfortunately, early attempts to develop potent in vivo BACE1 inhibitors were not successful, mainly due to poor brain penetration (Sinha, et al., 1999). Recently, poor blood–brain barrier penetration has been overcome with the development of potent third-generation small-molecule BACE1 inhibitors that exhibit satisfactory pharmacokinetics (PK) and robust cerebral Aβ reduction in preclinical animal models. As a result of these progresses, several BACE1 inhibitors have entered clinical studies in humans.

E2609 is a novel, small-molecule BACE1 inhibitor. Preclinical studies have shown that after oral dosing, E2609 inhibits the production of Aβ40 and Aβ42 in brain (rat and guinea pig) and in CSF and plasma (rat, guinea pig, and monkey). In humans, E2609 has been shown to inhibit BACE enzyme activity in CSF thereby lowering CSF levels of amyloid β, including Aβ(1-x), Aβ(1-40), and Aβ(1-42), both in vitro and in vivo in single ascending dose (SAD) and multiple (14 days) ascending dose studies (E2609 Investigator's Brochure). An ongoing study (study E2609-G000-202; Study 202) has yielded data in subjects with MCI due to AD /Prodromal AD and mild-to-moderate AD dementia (AD-D) administered oral doses of E2609. Interim study data indicated measurable levels of the BACE1 inhibitor in the CSF as well as inhibition of BACE activity and reduction of various forms of Aβ (eg, 1-x, 40, 42) after daily administration for 4 weeks.

This clinical study, E2609-G000-302 (Study 302), is 1 of 2 studies in the Phase 3 E2609 program, and is primarily designed to evaluate the efficacy, safety, and tolerability of E2609 in subjects with Early Alzheimer's Disease (EAD). Confirmation is also required that these subjects meet the NIA-AA core clinical criteria for MCI due to AD or Mild AD. This study is intended to be pivotal for registration and marketing for this patient population.

From a regulatory standpoint, the minimum duration of pivotal studies conducted with potential AD modifiers depends on the expected progression rate of the disease and the assumed activity of the experimental agent. In patients with mild to moderate AD, a treatment duration of 18 months would be expected. However, in prodromal disease stages, longer treatment duration is necessary. It is therefore suggested that the treatment duration for this study be 24 months.

7.1 Nonclinical and Clinical Safety Data

The toxicity of E2609 has been evaluated in oral repeated-dose toxicology studies of up to 26 weeks duration in rats and 39 weeks in cynomolgus monkeys. Nonclinical findings of note include immunologic-related findings at 30 mg/kg and above in monkeys (including 1 cytomegalovirus-related death at 60 mg/kg). An additional completed monkey immunology study suggested that lymphocytes and lymphocyte subsets may be suitable markers to monitor potential immunotoxicity or immunomodulation by E2609 in a clinical setting. Further details of the nonclinical data to date with E2609 can be found in the Investigator's Brochure.

The clinical program to date includes 8 Phase 1 studies and 1 Phase 2 study:

Study E2609-A001-001 (Study 001) was a randomized, double-blind and placebo-controlled, SAD study that investigated doses ranging from 5 to 800 mg in healthy adult subjects (aged 30 to 55 years) and elderly subjects (50 mg dose only, aged 65 to 85 years).

Study 002 was a randomized, double-blind and placebo-controlled multiple ascending dose (MAD) study in healthy male and female subjects aged 50 to 85 years. CSF was collected before and following the 14 days of dosing so as to assess the PK levels of E2609 and the pharmacodynamic (PD) effects on BACE activity and Aβ levels.

Study E2609-A001-003 (Study 003) was a single-center, open label study in healthy subjects investigating the effects of drug-drug interactions by itraconazole, rifampin, and donepezil on the PK properties of E2609. It also investigated the effects of E2609 on the PK properties of digoxin. The clinical phase has been completed and reporting is in progress.

Study E2609-A001-004 (Study 004) was a single-center, randomized, double-blind, placebo- and active-controlled, single dose, 4-treatment crossover study to evaluate the effects of E2609 on QTc interval in healthy subjects (thorough QT study). Two dose levels of E2609 were evaluated in this study, including a 50 mg therapeutic dose and a 200 mg supratherapeutic dose.

Study E2609-A001-005 was an open label, single-dose study to determine the metabolism and elimination of [^{14}C]E2609 in healthy male subjects (aged 18 to 55 years).

Study E2609-A001-006 (Study 006) was a randomized, placebo-controlled, single-dose study conducted at a single center to evaluate the safety, tolerability, PK, and PD of E2609 in healthy adult male Japanese and white subjects.

Study E2609-A001-007 (Study 007) was a single-center, open label, randomized, 3-treatment crossover study of single oral doses of a capsule formulation of E2609 under fasted conditions and a tablet formulation administered under fed and fasted conditions in healthy subjects to evaluate their relative bioavailability.

The Phase 1 study, Study E2609-A001-101 (Study 101) has been completed. This study was a randomized, double-blind, placebo-controlled, Bayesian adaptive design study in adults

aged 50 to 85 with subjective memory complaints and who qualified as having MCI or mild AD.

Study E2609-G000-202 (Study 202) is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day.

The safety data from the SAD and MAD studies are discussed below, with particular focus on the context of the nonclinical findings with E2609. The clinical safety data are described in more detail in the Investigator's Brochure.

In the SAD study, single doses were well tolerated. All treatment-emergent adverse events (TEAEs) were mild to moderate in severity, with no severe TEAEs. There were no dose-related trends in the incidence of AEs among subjects treated with E2609. In elderly subjects treated with 50 mg of E2609, tolerability was comparable to younger subjects. There were no specific AEs in elderly subjects which were evidently more frequent than in younger subjects. No serious adverse events (SAEs) were reported, and there were no clinically significant changes in mean laboratory safety parameters, vital signs, or electrocardiogram (ECG) parameters. The 800 mg (maximum) dose was associated with a small increase of QTcF from baseline (14.9 ms at 4 hours postdose), consistent with nonclinical findings. Overall the data suggested that a single dose of E2609 might reduce some lymphocyte subsets (eg, CD4 [T helper cells], CD8 [cytotoxic T cells]) but the effects were highly variable across doses and the findings were not conclusive. There were no trends to suggest that E2609 altered immunoglobulin (Ig) levels. There were no clinical manifestations in terms of primary infections or relapse of latent infections in subjects who received single doses of E2609. A single dose of E2609 up to 800 mg is not considered to pose clinical safety concerns with regard to immune function.

In the MAD study, AEs of interest included relapse of orolabial herpes, viral respiratory tract infection, drug rash, and abnormal dreams. More details are available in the Investigator's Brochure. In summary, E2609 administered at doses of 200 and 400 mg was associated with reductions in CD4 (T helper cells), CD8 (cytotoxic T cells), and CD19 (B cells) counts at Day 8. These reductions were more clearly evident by Day 15, consistent with a treatment by time interaction in the statistical analysis. There was evidence that the lower doses of 50 to 100 mg also caused some reduction in CD4 lymphocyte counts by Day 15. Doses above 100 mg appeared to be associated with greater reductions in CD4 and CD8 lymphocyte counts, which occurred earlier in the treatment period compared with the effects of 25 to 100 mg doses. These effects on lymphocyte counts gradually resolved from Day 20 to Day 35, which were 6 and 21 days, respectively, after administration of the last dose of E2609 on Day 14. Reductions in CD4 and CD8 lymphocyte counts at doses of 200 and 400 mg to a level close to or less than the lower limit of normal (LLN) could be associated with increased risk of developing relapse of orolabial herpes or other infections.

In Study 003, a drug-drug interaction study, PK results showed that itraconazole (a potent inhibitor of cytochrome P450 [CYP] 3A4 and carboxylesterase-2 [CES2]) caused a mild

increase (by approximately 70%) of the area under the concentration x time curve (AUC) of E2609. Rifampin (a potent CYP3A4 inducer) caused a mild decrease (by approximately 20%) of the AUC of E2609. Donepezil (a moderate CES2 inhibitor) caused a mild increase (by approximately 20%) of the AUC of E2609 when coadministered with E2609 but not when dosed at least 2 hours apart from E2609. E2609 (which inhibits the P-glycoprotein 1 transporter) did not affect the PK properties of digoxin. Nonclinical studies also indicated that other CYP pathways apart from CYP3A4 would not be major pathways of metabolism of E2609. Based on these results, it is not considered necessary to impose restrictions during E2609 treatment on the use of concomitant medications that may be CYP3A4 inhibitors or other CYP enzymes inhibitors. Similarly, it was also not considered necessary to restrict the use of concomitant medications which are inducers of CYP450 enzymes. Given the results of study 003 moderate to strong CES2 enzyme inhibitors are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit.

However, simvastatin use is permitted only with once daily evening administration. Simvastatin use is recommended with night time administration as physiological studies showed that most cholesterol is synthesized when dietary intake is at its lowest. It is therefore expected that the PK interaction between E2609 and simvastatin is minimized because simvastatin is thought to mainly inhibit CES2 in the intestine when E2069 will not be present as it will be administered in the morning.

Study 004, a thorough QT study, demonstrated that single doses of E2609 up to the supratherapeutic dose of 200 mg did not have any clinically meaningful impact on the QTcF, heart rate, PR, or QRS intervals. The results from the moxifloxacin arm of the study confirmed adequate assay sensitivity for the study to detect even a small effect on QTcF. There were no T wave morphology abnormalities observed. Although the exposure-QTc analysis of the plasma concentration and ΔΔQTcF (placebo-corrected change from baseline of QTcF) detected a small but statistically significant relationship, overall data confirmed that an effect of >10 ms could be excluded up to the 200 mg supratherapeutic dose of E2609. The effects of E2609 on QTcF were comparable between subjects with the slow NAT2 genotype and those with the rapid/intermediate NAT2 genotype, whether at 50 or 200 mg E2609. This indicated that the M5 metabolite, whose PK is strongly influenced by NAT2 genotype, did not contribute to the effects on QTcF.

Study 006, a Japanese bridging study, demonstrated that overall PK and plasma PD, measured as percentage reduction in Aβ(1-x) from baseline at a 50 mg dose, were comparable between Japanese and white subjects. As a result, no dose adjustment was necessary for dosing Japanese subjects. In addition, the overall PK results indicated that the E2609 plasma exposures (C_{max} and AUCs) were proportional to the dose in Japanese subjects between the dose range of 5 to 200 mg. The PD effects in plasma, expressed as the maximum plasma Aβ(1-x) absolute reduction from baseline (A_{max}) and the total response (absolute change from baseline in the plasma Aβ(1-x) $AUAC_{(0\text{-}144h)}$) increased with increasing dose from 5 to 200 mg in Japanese subjects. The single oral doses of E2609 were generally safe and well tolerated in healthy Japanese and white subjects. The AE profile in this study was comparable between Japanese and white subjects with a low incidence of

TEAEs. There were no AEs of special interest or viral infections. There were no effects of E2609 on clinical chemistry, hematology parameters, or vital signs in healthy Japanese and white subjects. There was no clinically meaningful effect on QTcF following administration of E2609 doses up to 200 mg based on the high precision QT analysis that demonstrated that the upper bound of predicted 90% CI of change from baseline in QTcF was below 10 ms. The relationship between the E2609 concentrations and QTcF effect was similar between Japanese and white subjects at the E2609 dose of 50 mg.

8 STUDY OBJECTIVES

8.1 Primary Objective

The primary objective of this study is:

- To determine whether E2609 is superior to placebo on the change from baseline in the Clinical Dementia Rating - Sum Of Boxes (CDR-SB) at 24 months in subjects with EAD

8.2 Secondary Objectives

The secondary objectives of this study are:

- To evaluate the safety and tolerability of E2609 in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to worsening of CDR scores in subjects with EAD
- To determine whether E2609 is superior to placebo on the time to conversion to dementia for subjects who were not clinically staged as having dementia at Baseline based on a clinical diagnosis evaluated every 3 months
- To determine whether E2609 is superior to placebo on the rate of change over time (mean slope) based on CDR-SB score over 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up) in subjects with EAD
- To determine whether E2609 is superior to placebo on the Alzheimer's Disease Assessment Scale-Cognition$_{14}$ (ADAS-cog$_{14}$), Mini Mental State Examination (MMSE), and Functional Assessment Questionnaire (FAQ) at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on the ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in subjects with EAD
- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in biomarkers that reflect disease progression (eg, cerebrospinal fluid [CSF] total tau [t-tau] and phosphorylated-tau [p-tau], amyloid PET, volumetric Magnetic Resonance Imaging [vMRI], and functional MRI [fMRI]) at 24 months
- To evaluate the population PK of E2609 in subjects with EAD

Biomarker Objectives

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity at 24 months in subjects with EAD as measured by task free fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of AD, as deemed appropriate

8.3 Exploratory Objectives

The exploratory objectives of this study are:

- To explore the relationship between exposure (in CSF, plasma) of E2609 with efficacy or safety endpoints, as deemed appropriate
- To evaluate whether E2609 is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies
- To evaluate whether E2609 is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item
- To evaluate whether E2609 is superior to placebo on overall health related quality of life (HRQoL) for subjects with EAD and study partners at 24 months as measured by the following outcome measures:
    a. EuroQol - 5 Dimensions (EQ-5D) (5 Level version will be used)
    b. Quality of Life in Alzheimer's Disease (QOL-AD)
- To evaluate whether E2609 is superior to placebo on study partner burden for subjects with EAD at 24 months as measured by the Zarit's Burden Interview

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This study is a 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in EAD including MCI due to AD (Albert, et al, 2011) and the early stages of mild AD. In addition, the MCI due to AD population will also be consistent with the research criterion for "Prodromal AD" (Dubois, et al. 2010) in that episodic memory will be impaired on a list learning task (ISLT). An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment. A total of 1330 subjects will be randomized, in a double-blind manner, to receive either placebo or E2609 50 mg per day (approximately 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use. The 7 levels of the region are:

1. North America
2. Western Europe (including Oceana region)
3. Eastern Europe
4. Japan
5. China
6. Other Asian countries
7. South America

The study is designed to have more frequent visits focused on safety assessments during the first 3 months of treatment.

Two longitudinal biomarker substudies will evaluate the effects of study treatment on the underlying pathophysiology of AD using amyloid PET and/or CSF biomarkers. Participation in the substudies is optional and will require specific consent that will not affect enrollment or treatment in the main study.

The maximum estimated duration for each subject on study is approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

The Core study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. All Screening Visit assessments must be completed in the tiers as instructed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. All subjects will be assessed for eligibility using cognitive assessments to confirm that subjects meet the diagnostic criteria for EAD including MCI due to AD and the early stages of mild

AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-Up Period will last for 12 weeks and is required for all subjects, regardless of whether they completed all 24 months of treatment or discontinued study drug early.

A futility analysis is planned when 30% subjects have completed 24 months. A blinded sample size re-estimation may also be performed if there is an indication that sample size assumptions need to be changed.

An independent data safety monitoring board (DSMB) will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. Details will be provided in the DSMB Charter.

An overview of the study design is presented in Figure 1

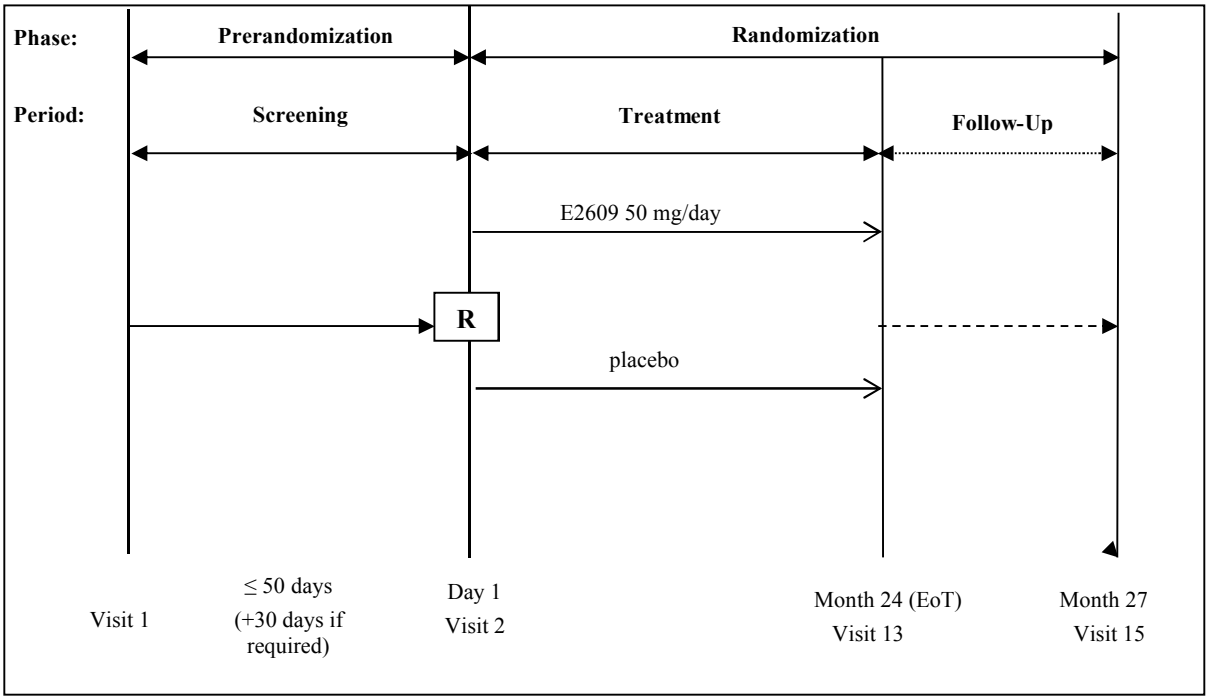

Figure 1 Study Design for E2609-G000-302

E2609 = Test drug, EoT = End of Treatment, R = randomization.

9.1.1 Prerandomization Phase

The Prerandomization Phase will last for up to 50 days plus an additional window of up to 30 days if required, and will include a Screening Period.

9.1.1.1 Screening Period

The purpose of the Screening Period is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3. No subject will undergo any further study procedures unless this informed consent has been obtained. Informed consent will also be obtained from the study partner, following a full explanation of their role in the study. The study partner need not be consented on the same day as the subject. Study partner consent must be obtained prior to the conduct of the CDR at the Screening Visit (Tier 1) which is the first study assessment that requires input from the study partner.

Subjects will also be informed about the optional CSF and PET longitudinal substudies. Subjects are able to consent to 1 or both substudies at any time from Tier 1 to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5, ie during the Randomization Phase of the study.

At all Screening Visit tiers, inclusion and exclusion criteria as described in Sections 9.3.1 and 9.3.2, respectively, will be assessed, prior and concomitant medications will be reviewed (see Section 9.4.7) and AEs will be assessed. The Screening Disposition electronic case report form (eCRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

9.1.1.1.1 TIER 1

Subject demography and medical history will be obtained before completing the following cognitive/clinical assessments: MMSE, International Shopping List Task (ISLT), CDR, and the modified Hachinski ischemic scale. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests as a common distractor task. It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments confirmed, prior to the CDR being administered. Subjects who are considered ineligible for the study based on these assessments should not continue with the rest of the Tier 1 assessments.

All subjects will be confirmed as meeting the diagnostic criteria for either MCI due to AD or the early stages of mild AD, and that they do not have other medical conditions which may interfere with study participation. The diagnosis and clinical disease staging will be verified

via a central review process, and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)). Confirmation of the diagnosis and clinical disease staging will not be required in order for the subject to progress to Tier 2 of the Screening Visit.

9.1.1.1.2 TIER 2

Tier 2 assessments may be started and/or completed on the same day as Tier 1 assessments, but only after all Tier 1 assessments have been completed and eligibility to continue confirmed. Tier 2 assessments comprise the Columbia Suicide Severity Rating Scale (C-SSRS) and the following quality of life assessments:

- EQ-5D: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner
- QOL-AD: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner
- Zarit's Burden Interview: this is an assessment of the study partner.

The quality of life assessments conducted at Screening Visit 1, Tier 2 will act as the baseline measures for the study.

9.1.1.1.3 TIER 3

Tier 3 assessments may be started and/or completed on the same day as Tier 2 assessments, but only after all Tier 2 assessments have been completed and eligibility to continue confirmed. Tier 3 assessments include a complete physical examination with dermatologic review, a full neurologic exam, measurement of vital signs (body temperature, sitting heart rate, and sitting BP), measurement of height and weight, and a single 12-lead ECG. Blood samples will be taken for measures of clinical chemistry, hematology, thyroid function, vitamin B12, and for a viral screen. Blood samples will also be taken for pharmacogenomic (PGx) analyses, PD, exploratory biomarker assays, and for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood mononuclear cell (PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. A urine sample will also be taken in order for urinalysis to be conducted. Finally, a serum pregnancy test will be conducted for females of child-bearing potential.

9.1.1.1.4 TIER 4

Tier 4 may only be started following the confirmation of eligibility from the results of the assessments performed in all of the preceding tiers of screening. Tier 4 comprises an MRI scan for brain abnormalities which may exclude study participation. Additional scanning sequences for vMRI and fMRI assessments will be run immediately following the eligibility MRI sequences in all subjects. The MRI assessments conducted during Screening will also be used as the baseline MRI assessments for the respective measures.

9.1.1.1.5 TIER 5

Tier 5 procedures may only be performed following confirmation of eligibility from the MRI conducted at Tier 4. Subjects who have met all eligibility criteria thus far, will be assessed for biomarkers of brain amyloid pathology with either amyloid PET (Screening amyloid PET) or cerebrospinal fluid Aβ(1-42) (Screening CSF) or both. Amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility (evidence of amyloid pathology). For those subjects who consent to both CSF and PET eligibility assessments the 2 assessments should be separated by at least 24 hours with CSF collected before PET assessment. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result).

Screening amyloid PET and/or Screening CSF (amyloid, t-tau, p-tau) will serve as the baseline data for subjects who consent to the amyloid PET and CSF longitudinal substudies respectively. Subjects who complete amyloid PET and/or CSF assessments to confirm amyloid pathology for study eligibility are not required to participate in the respective longitudinal substudies

9.1.2 Randomization Phase

The Randomization Phase consists of a Treatment Period (24 months) and a Follow-Up Period (3 months). All screening assessments must be completed, and eligibility to continue in the study confirmed, before any Visit 2 assessments commence. Visit 2 (Randomization) should occur as soon as possible after completion of all screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

During the Randomization Phase all subjects will undertake assessments of cognition, daily function, quality of life, safety, PK, and PD, while those subjects who consent to participate in the amyloid PET and/or CSF longitudinal substudies will undertake additional amyloid PET and/or CSF assessments as indicated in the protocol. (Refer to Table 3 for full details of the assessments and procedures to be performed at each visit in the Randomization Phase.)

9.1.2.1 Treatment Period

During Visit 2, the following assessments will be completed before the subject receives their first dose of study drug: MMSE, CDR, ADAS-cog$_{14}$, FAQ, and NPI-10. These assessments will provide baseline measurements for the study. Inclusion and exclusion criteria will again be reviewed together with concomitant medications and assessment of AEs. A single 12-lead ECG will be conducted. All ECG recordings will be evaluated by a central reader. The Columbia-Suicide Severity Rating Scale (C-SSRS) will also be administered. A baseline routine physical examination with dermatologic review, vital signs measurements, clinical laboratory testing (including viral characterization), urinalysis using urine dipstick, and a urine pregnancy test (females of child bearing potential only), will be performed. Additional blood samples will be taken for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated peripheral blood monocytes

(PBMCs) which will be stored for later testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study. Whilst there is no prescribed order in which the assessments at each visit are to be performed, the subject component of the cognitive, functional and quality of life assessments are to be performed in the morning whenever possible, or consistently at the same time of the day and ideally should be completed before the more invasive procedures (eg, physical examination, ECG, blood draw).

Subjects will be randomized at Visit 2 (Day 1) to receive E2609 50 mg per day or placebo administered orally QD in the morning with or without food. Subjects will be encouraged to stay at the site for an appropriate period of time for observation following their first dose of study drug. Double-blinding to study drug will be in effect throughout the Treatment Period.

The CDR will be conducted every 3 months during the Core Study; other cognitive and functional assessment instruments will be administered every 6 months. Every 3 months, the investigator is required to confirm the clinical staging of AD (ie, dementia or nondementia). This staging decision will be verified via a central review process and adjudicated if necessary (adjudication will only occur when there is a discrepancy between the clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s)).

The health-related quality of life measures will be conducted every 6 months during the Core Study, along with the NPI-10.

MRI scans (including vMRI and fMRI) will be performed at 12 and 24 months during the Core Study or at the ED visit.

At every visit, AEs will be assessed, concomitant medications will be reviewed, physical examinations with dermatologic review by the study investigator will be performed, vital signs and respiratory rate will be measured, suicidality will be assessed, blood will be drawn for clinical chemistry, hematology, and for immunologic assessments. A urine sample will be provided for dipstick urinalysis. Other assessments, including safety assessments (neurologic exams, ECGs, urine pregnancy tests for females of child-bearing potential), and blood draws for PK, PD and assessment of immune status are performed at different intervals throughout the treatment period of the study.

For subjects who consent to the amyloid PET longitudinal substudy, amyloid PET will be conducted after 12 and 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). For subjects who consent to the CSF longitudinal substudy, CSF will be collected after 24 months of treatment during the Core Study (or at the ED visit, provided the subject has received at least 39 weeks of study drug). Please refer to Schedule of Assessments (Table 3).

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.2.2 Follow-Up Period

All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 post-treatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as unscheduled (UNS) assessments or visits during the post-treatment follow-up period.

In some cases, UNS visits will be needed to follow-up on safety or other findings, and the related assessments (outlined in the Schedule of Assessments) will depend on the reason for the UNS visit, and will be decided at the discretion of the investigator.

9.1.3 Extension Phase

An open-label Extension Phase will be available for subjects who complete the full 24 months of treatment in the Core study. The Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated. Full details of the Extension Phase will be available in a future protocol amendment.

9.2 Discussion of Study Design, Including Choice of Control Groups

9.2.1 Overview

This study is a multicenter, multiple-dose, double-blind, placebo-controlled, parallel-group study in subjects with EAD including MCI due to AD and the early stages of mild AD, aiming to randomize a total of 1330 subjects across 2 treatment groups, (placebo, 50 mg per day E2609) for 24 months. The maximum estimated duration for each subject on study is anticipated to be approximately 29 months (ie, 2-month Prerandomization Phase, followed by 24 months of treatment and a 3-month Follow-Up Phase).

As currently there is no cure for AD, there is no active or positive control for this study as at this time, no known way of slowing the progression of this disease, and no approved treatment available to reverse the deterioration of AD.

The primary endpoint of this study is to evaluate the effects of E2609 compared to placebo on the CDR-SB score. This endpoint is widely used in AD trials as a global measure of disease progression. The instrument is rated after a semi-structured interview with the subject and a study partner, and does not directly rely on psychometric tests, thus avoiding learning effects. One important factor associated with the use of the CDR–SB is that it is designed to incorporate cognitive and functional components; changes in the CDR-SB score reflect changes in both components. The clinical researcher separately interviews the subject and a study partner in order to assess changes in the subject's performance relative to their premorbid performance on 6 domains: memory, orientation, judgment and problem solving; community affairs, home and hobbies, and personal care. Each domain is scored as 0 (none), 0.5 (questionable) except for personal care, 1.0 (mild), 2.0 (moderate), or 3 (severe). Two overall scores can be derived – a calculated global score using a standardized algorithm and a

cumulative score summing the boxes. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations.

Additional secondary endpoints of the study will evaluate the effects of E2609 compared to placebo on time to disease progression, time to conversion to dementia, the ADAS-cog$_{14}$ (including a separate endpoint for the immediate recall and delayed recall subtests), MMSE, and FAQ at 24 months. These scales are also widely used and well recognized instruments in AD trials.

Additional important biomarker endpoints will evaluate the AD modifying properties of E2609 by assessing several human AD biomarkers. Of note, there is no widely recognized consensus over the utilization of a single AD biomarker as a measure of disease modification. Therefore, it is proposed that several biomarkers will be utilized during this study without a specific hierarchical approach.

The proposed biomarkers for this study are aimed at evaluating the effects of E2609 on disease progression and correlating these with clinical benefit. An additional aim is to determine whether inhibition of amyloid production by E2609 has downstream effects on neurodegeneration (as measured by CSF and brain tau levels that are thought to be associated with neurofibrillary pathology), especially in the EAD population. The final aim of the biomarker strategy for this study is to determine whether inhibition of amyloid production by E2609 increases the non-amyloidogenic secretase pathway, and to determine whether such an effect could potentially slow the disease and show benefit on cognition.

Randomization and stratification will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints.

Rationale for the selection of doses used in the study is provided in Section 9.4.4.

9.2.2 Rationale for Study Population

This study will enroll subjects with EAD including MCI due to AD and the early stages of mild AD. It is considered that this population is the most likely to benefit from the administration of a BACE1 inhibitor such as E2609. This is because as AD progresses to the clinical diagnosis of dementia and more severe stages of the disease with the loss of functional capabilities, the amyloid load in the brain has already reached a plateau and significant neurodegeneration has occurred (Jack et al., 2011). There is a growing consensus within the AD field that it may be necessary to initiate disease-modifying treatments earlier, before the onset of clinical dementia (Aisen et al., 2010). As a consequence, attempts to slow disease progression with E2609 are most likely to succeed at an earlier stage at which there is limited neurodegeneration; therefore, the selected population for this study is subjects with EAD including MCI due to AD and the early stages of mild AD.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.2.3 Rationale for Clinical Endpoints

The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment effects in AD. The cumulative score or CDR-SB is a well-described, validated, and reliable measure of change through the course of AD and has been proposed as a suitable single outcome measure for AD trials in dementia and pre-dementia populations (FDA 2013 AD Guidelines, EMA 2016 AD Guidelines).

The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). Furthermore, a separate endpoint for the ADAS-cog$_{14}$ immediate recall and delayed recall subtests is included.

The MMSE is a cognitive instrument commonly used for screening purposes, for staging of disease severity and is often measured longitudinally in AD clinical studies to follow disease progression and treatment effects (Folstein, et al., 1975).

The FAQ collects information on 10 items concerned with performing daily tasks necessary for independent living. The FAQ is considered as a better indicator of clinical meaningfulness than cognitive change as it reflects the subject's functional state and should correlate well with AD progression.

The ISLT is sensitive to memory impairment that characterizes both AD and MCI (Lim, et al., 2012a). In MCI subjects, the magnitude of the impairment observed on the total recall and delayed recall trials of the ISLT was consistent with the magnitude of impairment expected to occur. It is sensitive to the episodic memory impairment that characterizes MCI with high amyloid (unpublished data from the Australian Imaging, Biomarker & Lifestyle Flagship Study of Ageing study). Data are robust across different groups of healthy older individuals, and accordingly criteria used for defining abnormal performance are reliable (Thompson, et al., 2011; Lim, et al., 2012a; Lim, et al., 2012b). Data computations indicate that the ISLT will be sensitive to the expected changes in amyloid-related memory dysfunction with E2609 treatment.

9.2.4 Rationale for Biomarkers

The biomarker strategy for this study includes the following aims:

- To determine whether E2609 is superior to placebo on brain amyloid levels at 24 months as measured by amyloid PET in subjects with EAD

- To determine whether E2609 is superior to placebo on CSF t-tau and p-tau levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on CSF amyloid beta (Aβ) levels at 24 months in subjects with EAD
- To determine whether E2609 is superior to placebo on hippocampal atrophy at 24 months in subjects with EAD as measured by changes in hippocampal volume using vMRI
- To evaluate whether E2609 is superior to placebo in preserving connectivity as measured by fMRI
- To explore the relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of AD as deemed appropriate

CSF biomarkers and amyloid PET assessments on disease progression at 24 months (and at 12 months for amyloid PET) will be evaluated in a substudy of subjects. The CSF substudy is limited to a single timepoint at 24 months to acknowledge the additional burden to the subject that a lumbar puncture procedure entails. Participation in the substudies is optional and will require specific consent.

These aims are discussed below in the context of the individual biomarker assessments to be used in this study.

Briefly, the biomarkers that will be utilized and assessed during this study are:

Soluble Biomarkers in CSF

Aβ(1-x) captures the effect on the total Aβ component; therefore, the measurement of this Aβ isoform most appropriately represents the total pharmacologic effect (Aβ[1-40] + Aβ [1-42] and other C-terminally truncated Aβ peptides such as Aβ[1-38]) on inhibition of BACE enzyme cleavage.

Aβ(1-42) measurements in CSF have shown high correlation with results using 11C-Pittsburgh Compound B (PiB), suggesting that CSF Aβ(1-42) reflects fibrillar Aβ content (Grimmer, et al., 2009). The aggregation of Aβ peptides into plaques, and subsequent retention of peptides in the brain parenchyma, accounts for reduced availability of Aβ to diffuse into the CSF. The decreases seen in AD due to amyloid plaque deposits are related to this decrease.

T-tau and p-tau are sensitive markers of axonal and neuronal degeneration (t-tau) and NFTs (p-tau), and have been demonstrated to increase in parallel with disease progression (Chintamaneni, et al., 2012).

Baseline levels of Aβ(1-42), t-tau, and p-tau will also help elucidate the extent of AD pathology at study entry, and can be combined with *ApoE4* genotype in addition to the

baseline imaging variables to help explain differences in treatment response between subjects.

Amyloid PET

Amyloid PET imaging will be performed in this study for 2 primary reasons: 1) as one of the methods of confirming the presence of amyloid pathology in the brain of subjects with EAD including MCI due to AD and the early stages of mild AD at study entry (the other method being measurement of Aβ(1-42) in the CSF); and 2) to evaluate the effects of E2609 on amyloid levels in the brain at 12 and 24 months, both by whole brain analysis (the average of 5-6 cortical regions) and brain region analysis. This second part is an optional longitudinal substudy.

vMRI and fMRI

vMRI performed at 12 and 24 months will be used to evaluate the effects of E2609 on rates of atrophy across the treatment groups and to provide support that effective treatment is associated with modification of disease progression. A large body of data has shown that structural MRI reliably tracks disease progression in AD. Atrophy tends to occur preferentially in the lateral temporal and posterior parietal regions during the early stages of disease and progresses towards the anterior regions of the brain (frontal cortex) in its later stages. For this reason hippocampal volume has been selected as a secondary endpoint, and it is predicted that clinically efficacious doses will be associated with a slowing in the rate of hippocampal atrophy compared to rates observed in the placebo. Whole brain, ventricular volumes, and possibly other regions deemed to be of scientific value will also be measured.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. fMRI eliminates performance confounds that are seen with task based functional neuroimaging. fMRI requires an additional 7 to 10 minutes of scan time for acquisition of the data. fMRI data will be used to generate connectivity maps based on critical anatomical regions (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

9.3 Selection of Study Population

Approximately 1330 subjects with EAD including MCI due to AD and the early stages of mild AD will be enrolled across up to approximately 350 centers worldwide. Randomization will be stratified according to region (7 levels), clinical dementia staging, with no more than approximately 25% of the randomized subjects diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

Subjects who do not meet all of the inclusion criteria or who meet any of the exclusion criteria will not be eligible to receive study drug.

9.3.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in this study:

1. MCI due to AD or Mild AD according to the National Institute of Aging – Alzheimer's Association (NIA-AA) core clinical criteria and must have all of the following:
   a. MMSE score equal to or greater than 24
   b. CDR global score of 0.5
   c. CDR Memory Box score of 0.5 or greater
2. A history of subjective memory decline with gradual onset and slow progression over the last 1 year before Screening; this MUST be corroborated by a study partner
3. Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT.
4. Positive biomarker for brain amyloid pathology as indicated by at least 1 of the following:
   a. PET assessment of amyloid imaging agent uptake into brain. Note: amyloid PET screens will be performed according to local regulatory guidelines and thus may be restricted for those subjects who are not suitable for LP to obtain CSF for testing of eligibility.
   b. CSF assessment of Aβ(1-42)

   NOTE: Subjects may undergo both the amyloid PET and CSF assessments, but need a positive amyloid result in only 1 of the 2 procedures to confirm eligibility. Subjects who consent to amyloid PET or CSF for eligibility purposes are not required to participate in the amyloid PET or CSF longitudinal substudies. Use of a historical amyloid PET (conducted within 12 months before the planned date of randomization) is acceptable for determination of eligibility but will not suffice for the baseline assessment if the subject wishes to consent to the amyloid PET longitudinal substudy. The historical imaging data must be made available to the sponsor.
5. Male or female subjects between 50 and 85 years of age, inclusive at the time of consent
6. If receiving an AChEI or memantine or both for AD, must be on a stable dose for at least 12 weeks prior to Randomization. Treatment-naïve subjects with AD can be entered into the study.
7. Subjects must have been on stable doses of all other (ie, non-AD related) permitted concomitant medications for at least 4 weeks prior to Randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a Pro re nata (PRN) basis. Subjects who require a short course of treatment, such as anti-infectives or oral steroids, may be randomized once the acute illness has completely resolved, even if the concomitant medication continues.
8. Must have an identified study partner (defined as a person able to support the subject for the duration of the study and who spends at least 8 hours per week with the subject). The study partner must provide written informed consent. In addition, this person must be willing and able to provide follow-up information on the subject throughout the course of the study. This person must, in the opinion of the investigator, spend sufficient time with the subject on a regular basis such that they can reliably fulfill the requirements of being a study partner. A study partner need not be living in the same residence with the subject. For such a study partner not residing with the subject, the investigator has to be

satisfied that the subject can contact the study partner readily during the times when the study partner is not with the subject. Study partners need to provide input to the following assessments: CDR, FAQ, EQ-5D, QOL-AD, Zarit's Burden Interview, NPI-10, and the clinical assessment of suicidality. Consideration can occur for the investigator to decide whether the study partner can provide information over the telephone or whether the study partner must attend the study visits in person with the subject.

9.3.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from this study:

1. Females who are breastfeeding or pregnant at Screening or Baseline (as documented by a positive beta-human chorionic gonadotropin test. A separate baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug. Females of childbearing potential who:
   - Within 28 days before study entry, did not use a highly effective method of contraception, which includes any of the following:
     - o total abstinence (if it is their preferred and usual lifestyle)
     - o an intrauterine device or intrauterine hormone-releasing system
     - o an oral contraceptive (Subject must be on a stable dose of the same oral contraceptive product for at least 28 days before dosing and throughout the study and for 28 days after study drug discontinuation.)
     - o have a vasectomized partner with confirmed azoospermia
   - Do not agree to use a highly effective method of contraception (as described above) throughout the entire study period and for 28 days after study drug discontinuation.

   For sites outside of the European Union, it is permissible that if a highly effective method of contraception is not appropriate or acceptable to the subject, then the subject must agree to use a medically acceptable method of contraception, ie, double-barrier methods of contraception such as condom plus diaphragm or cervical/vault cap with spermicide.

   NOTE: All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group, and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy, or bilateral oophorectomy, all with surgery at least 1 month before dosing)

2. Any condition that may be contributing to cognitive impairment above and beyond that caused by the subject's AD

3. Subjects with a history of seizures within 5 years of Screening or subjects with disturbance likely to be due to seizures within 5 years of Screening

4. History of transient ischemic attacks (TIA) or stroke within 12 months of Screening

5. Modified Hachinski Ischemia Score greater than 4 at Screening

6. Any of the following psychiatric symptoms:

   - Psychiatric diagnosis or symptoms, (eg, hallucinations, major depression, or delusions) that, in the opinion of the investigator, could interfere with study procedures

   - Has a "yes" answer to C-SSRS suicidal ideation items 4 or 5, or any suicidal behavior within 6 months before Screening, at Screening, or at the Randomization Visit, or has been hospitalized or treated for suicidal behavior in the past 5 years before Screening

7. Have any contraindications to MRI scanning, including cardiac pacemaker/defibrillator, ferromagnetic metal implants (eg, in skull and cardiac devices other than those approved as safe for use in MRI scanners) or

   - Have any evidence of other clinically significant lesions that could indicate a dementia diagnosis other than AD on brain MRI at Screening.

   - Exhibit other significant pathological findings on brain MRI at Screening, including but not limited to: an area of superficial siderosis; evidence of cerebral vasogenic edema; evidence of cerebral contusion, encephalomalacia, aneurysms, vascular malformations, or infective lesions; evidence of multiple lacunar infarcts or stroke involving a major vascular territory, severe small vessel, or white matter disease; space occupying lesions; or brain tumors (however, lesions diagnosed as meningiomas or arachnoid cysts and less than 1 cm at their greatest diameter need not be exclusionary).

8. Subjects who undergo CSF LP procedure with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or International Normalized Ratio [INR] >3)

9. Results of laboratory tests conducted during screening that are outside the following limits:

   - Absolute lymphocyte count below Lower Limit of Normal (LLN) or below 800 per mm^3 (whichever is higher)

   - Thyroid stimulating hormone (TSH) above normal range. Other tests of thyroid function with results outside the normal range should only be exclusionary if they are considered clinically significant by the investigator (this applies to all subjects whether or not they are taking thyroid supplements)

   - Abnormally low (below LLN) serum Vitamin B12 levels (if subject is taking Vitamin B12 injections, level should be at or above the LLN)

10. Subjects at risk of increased risk of infection, specifically:

- Subjects with chronic viral hepatitis, a history of active tuberculosis disease (TB), ophthalmic shingles or ocular herpes simplex virus (HSV) infection

- Any active infection within the last 4 weeks before randomization. For such cases, the timing of randomization can be extended (up to 4 weeks) to allow the infection to resolve

- Any immunological disease which is not adequately controlled, or which requires treatment with biologic drugs during the study. History of immunoglobulin deficiency or other immunodeficiency disorders (including subjects known to be HIV positive)

11. Have received any live/live attenuated vaccine in the 3 months before randomization

12. Any chronic inflammatory disease that is not adequately controlled or that requires systemic or ocular immunosuppressive or immunomodulatory therapy.

    NOTE: The following subjects do not need to be excluded:

    - Subjects with seasonal or perennial allergic rhinitis, asthma, or chronic obstructive pulmonary disease where the condition is considered to be stable and adequately controlled by inhaled steroids.

    - Hashimoto's thyroiditis but who are stable on thyroid replacement therapy and not on systemic immunosuppressive therapy.

    - Cutaneous manifestations of immunological disease that do not require systemic immunosuppressive therapy or systemic immunomodulatory therapy (ie, topical steroid treatment is permitted)

13. Any other clinically significant abnormalities, such as:

    - Physical examination, vital signs, laboratory tests or ECG at Screening or Baseline which in the opinion of the investigator require further investigation or treatment or which may interfere with study procedures or safety.

    - Other medical conditions (eg, cardiac, respiratory, gastrointestinal, psychiatric, renal disease, severe hepatic impairment) which are not adequately and stably controlled, or which in the opinion of the investigator(s) could affect the subject's safety or interfere with the study assessments

    - Illiteracy, or severe visual or hearing impairment that would prevent the subject from performing psychometric tests accurately

14. A prolonged QTc interval calculated using Fridericia's formula (QTcF) interval (QTcF greater than 450 ms). If the QTcF is greater than 450 ms on the first single 12-lead ECG,

2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated.

15. Malignant neoplasms within 5 years of Screening (except for basal or squamous cell carcinoma in situ of the skin, or localized prostate cancer in male subjects with treatment cycles completed at least 6 months prior to screening). Subjects who had malignant neoplasms but who have had at least 5 years of documented uninterrupted remission before Screening need not be excluded.

16. Hypopigmentation conditions (eg, albinism and vitiligo). Hypopigmentation associated with scarring need not be exclusionary

17. Known or suspected history of drug or alcohol abuse or dependence within 2 years before Screening

18. Taking prohibited medications

19. Have participated in a clinical study involving:

    - any therapeutic monoclonal antibody, protein derived from a monoclonal antibody, immunoglobulin therapy, or vaccine within 6 months before Screening for whom it cannot be documented that they were randomized only to placebo or never received study drug

    - E2609

    - any new chemical entity for AD with last study drug dose occurring within 6 months prior to Screening unless it can be documented that the subject received only placebo

    - any other investigational medication (unless it can be documented that the subject received only placebo) or device within 8 weeks or 5 half-lives (whichever is longer) before randomization

20. Planned surgery which requires general, spinal or epidural anesthesia that would take place during the study. Planned surgery which requires only local anesthesia and which can be undertaken as day case without inpatient stay postoperatively need not result in exclusion if in the opinion of the investigator this operation does not interfere with study procedures and subject safety.

9.3.3 Removal of Subjects from Therapy or Assessment

The investigator may withdraw the subject from the study at any time for safety or administrative reasons. The subject may stop study drug or withdraw from the study at any time for any reason.

Absolute lymphocyte count from the hematology and differential panel will be monitored during the study. Should a subject develop a Grade 2 or greater lymphocytopenia (less than

800/mm^3), this should be confirmed as soon as possible but no later than within 5 days with a repeat test of absolute lymphocyte count. If confirmed, study drug administration should be interrupted for a minimum period of 2 weeks and for a maximum period of 4 weeks. Restart of study drug may take place only when absolute lymphocyte count returns to greater than LLN. Absolute lymphocyte count will be measured 4 weeks after restart of study drug. Subsequent measurements of absolute lymphocyte counts will follow the schedule of assessments (Table 3) and any results showing a Grade 2 or greater lymphocytopenia (less than 800/mm^3) should be handled as above. If a 2nd occurrence of Grade 2 or greater lymphocytopenia (less than 800/mm^3), that is confirmed on repeat testing, occurs within 6 months, then the subject should be discontinued permanently from the study drug.

Subjects who discontinue study drug early must complete the ED Visit (within 7 days of the last dose of study drug) and the Follow-Up Visits (1 and 3 months after the last dose of study drug). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12-month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their regularly scheduled clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition.

The primary reason for discontinuation and all other reason(s) contributing to the subject's discontinuation from study drug(s) should be collected on the ED from study drug electronic case report form (eCRF) page. In addition, the date of last dose of study drug(s) will be recorded on the Study Drug Dosing eCRF page. If a subject discontinues study treatment and the study at the same time, the end-of-study procedures (Final Visit) will be followed (see Section 9.5.5).

9.4 Treatment(s)

9.4.1 Treatment(s) Administered

For this study the test drug is E2609 and the control drug is placebo. All study drug is to be administered orally, once daily (QD), in the morning with or without food. As shown in Figure 1, there will be 2 treatment arms where the E2609 arm will be administered a single dose of 50 mg per day and the control arm will be administered placebo.

Study treatment will begin on Day 1 (at the study site) following randomization and will continue for approximately 24 months. Please refer to Table 3 and Section 9.5.1.4.1 for specific information regarding study drug administration on days when PK sampling is to be performed.

Study drug dose will remain the same for each individual subject throughout the duration of the study. If a subject develops a concurrent illness during the treatment period, the investigator should discuss with the medical monitor on whether dosing with study drug needs to be temporarily suspended. As a general clinical guideline, dosing with study drug may be resumed after resolution or stabilization of the concurrent illness, after discussion with the medical monitor.

Rules for discontinuing study treatment for subjects due to skin rash or to severe infections are described in Section 9.5.1.5.5.

9.4.2 Identity of Investigational Product(s)

E2609 will be supplied by the sponsor as tablets of 50-mg dose strength in bottles of 35 tablets each. Placebo tablets to match E2609 will be of identical appearance. Each subject will receive 1 tablet of 50 mg E2609 or an identical placebo tablet, to be administered orally QD in the morning with or without food. The product release certificates for E2609 and placebo will be included in the clinical study report for this protocol.

Subjects will be stratified and randomized, and drug will be dispensed, via an interactive voice and web response system (IxRS) system (see Section 9.4.3).

The sponsor will provide the study drugs packaged in a double-blind configuration. Each subject's study tablets will consist of either E2609 or placebo (see Section 9.4.2.3 for labeling details).

9.4.2.1 Chemical Name, Structural Formula of E2609

- Test drug code: E2609
- Generic name: not applicable
- Chemical name: International Union of Pure and Applied Chemistry
  N-{3-[(4a*S*,5*R*,7a*S*)-2-Amino-5-methyl-4a,5-dihydro-4*H*-furo[3,4-*d*][1,3]thiazin-7a(7*H*)-yl]-4-fluorophenyl}-5-(difluoromethyl)pyrazine-2-carboxamide
- Molecular formula: $C_{19}H_{18}F_3N_5O_2S$
- Relative molecular mass: 437.44

9.4.2.2 Comparator Drug

Not applicable.

9.4.2.3 Labeling for Study Drug

E2609 will be labeled in accordance with text that is in full regulatory compliance with each participating country and is translated into the required language(s) for each of those countries. The following information may be included but is not limited to:

- Protocol number
- For clinical study use only
- Name and address of the sponsor
- Chemical name/drug identifier
- Lot number/batch number
- Storage conditions, expiration date if necessary

9.4.2.4 Storage Conditions

Study drug will be stored in accordance with the labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained; the temperature should be monitored continuously by using either an in-house validated data acquisition system, a mechanical recording device, such as a calibrated chart recorder, or by manual means, such that minimum and maximum thermometric values over a specific time period can be recorded and retrieved as required.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study. The doses and number of treatment groups to be used are described in Section 9.4.1.

Stratification and randomization will be performed centrally by an IxRS. The IxRS or clinical supply vendor will generate the randomized bottle identification numbers. At enrollment (Screening), the investigator or designee will call the IxRS to register the subject information. At randomization (Visit 2), the IxRS will assign each subject a unique randomization number.

9.4.4 Selection of Doses in the Study

Selection of E2609 50 mg per day is based on the results (PD, safety, and tolerability) from the completed Phase 1 studies and interim data from the ongoing Phase 2 Study 202. Study 202 is currently evaluating the PD effects (reduction from baseline in CSF Aβ levels) of 5, 15, and 50 mg of E2609 given daily. An interim PD analysis has been performed on the degree of CSF Aβ reduction achieved with E2609 5, 15, and 50 mg per day. Based on these results E2609 50 mg per day produced relatively high levels of CSF Aβ reduction (greater than 50%) and this, in turn, should translate into greater clinical benefit while minimizing the safety concerns. Based on these data, E2609 50 mg per day dose was selected as a viable dose for this study. Subjects will be stratified according to region (7 levels), clinical dementia staging with no more than approximately 25% of the randomized subjects

diagnosed with the early stages of mild dementia due to AD, and concurrent AD medication use.

9.4.5 Selection and Timing of Dose for Each Subject

E2609 is administered orally, QD, in the morning with or without food. Study treatment will begin on Day 1 following randomization and will continue for 24 months.

9.4.6 Blinding

E2609 and placebo will be administered as tablets of identical appearance.

During the Randomization and Follow-Up Phases, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes (double-blind). Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO, and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per the standard operating procedure.

PK and PD data will be provided to the sponsor by the PK and PD analysis laboratories using dummy subject numbers instead of actual subject numbers. The same dummy subject number will be used for a subject's PK and PD data. These data will be used to evaluate whether the PK and PD effects seen in this study are similar to those seen in previous studies. Thereafter, unblinded PK and PD data will only be provided to the sponsor after study completion.

In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.5. If possible, before breaking the blind, the investigator should consult with the sponsor to ascertain the necessity of breaking the code. If an AE results in the investigator breaking the blind, then that AE must be reported as a SAE.

9.4.7 Prior and Concomitant Therapy

Any medication (including over-the-counter medications) or therapy administered to the subject prior to the study (within 6 months of randomization) and during the study (starting at the date of informed consent) will be recorded on the Prior & Concomitant Medication eCRF or Non-Pharmacological Procedures eCRF. The investigator will record on the Adverse Event eCRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition eCRF.

Listings of prohibited and permitted drugs are provided in Appendix 2 (Prohibited medications are presented in Listing 1, Listing 2, and Listing 3. Medications that are permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6).

The following agents are not permitted before randomization (specific time frames are shown below) and throughout the study:

a) Immunoglobulin therapy and biologic drugs are not permitted within 6 months before Screening
b) Systemic or ocular immunosuppressive or immunomodulatory drugs are not permitted for a period of 5 half-lives or 60 days (whichever is longer) before randomization
c) Moderate to strong inhibitors of carboxylesterase 2 (CES2) enzyme activity are not permitted for a period of 5 half-lives or 7 days (whichever is longer) before randomization and until the last treatment visit. Simvastatin use is permitted only with QD evening administration.

Concomitant therapy with AChEI or memantine should only be allowed and/or acceptable for the region or country in which the study is being conducted. Subjects who are taking AChEI or memantine will be required to be on a stable dose for at least 12 weeks before randomization. Initiation of therapy or changing dose of AChEIs or memantine during the study should not be undertaken unless, for each subject, disease progression reaches a clinically significant medical threshold that requires additional symptomatic treatment. Subjects who start on AChEI or memantine or change their dose during the Treatment Period will be permitted to continue in the study; however, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

Subjects who are taking other medications will be required to be on a stable dose for at least 4 weeks before randomization, except for medications which are administered as short courses (eg, up to 3 weeks unless discussed and agreed with Medical Monitor) of treatment (eg, anti-infectives, oral steroids) or which are to be used on a PRN basis. Concomitant medications (including benzodiazepines and opiates) which are used on a PRN basis and which are central nervous system (CNS) active and may affect cognitive function are not permitted during a period of 72 hours prior to cognitive testing.

For subjects who undergo an LP for collection of CSF: Subjects who are on anticoagulants may have a variable dose but should have stable anticoagulation control for at least 4 weeks before the LP procedure. Subjects may be required to stop their anticoagulant medication prior to CSF collection and then restart this medication after the LP procedure, as per local guidelines.

Either aspirin or clopidogrel (or any other antiplatelet drug which is not aspirin) is permitted in all subjects. Aspirin and clopidogrel (or any other antiplatelet drug which is not aspirin) in combination are also permitted but subjects who are on such a combination of antiplatelet drugs may be required to stop 1 or more of these antiplatelet drugs before the LP procedure and restart after the LP as per local guidelines.

Subjects who initiate treatment with drugs not intended for treatment of cognitive impairment during the study should continue in the study if in the opinion of the investigator this will not interfere with study procedures or subject safety and are not prohibited above. However, if such drugs may affect cognitive function, subjects should not undertake cognitive assessments until they have been on a stable dose for at least 4 weeks.

9.4.7.1 Drug-Drug Interactions

Listings of prohibited drugs are provided in Listing 1, Listing 2, and Listing 3.

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the Treatment Period of the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study
- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated Food and Drug Administration (FDA) Form FDA 1572, where applicable
- Financial Disclosure form(s) for the principal investigator and all subinvestigators listed on Form FDA 1572, where applicable
- A signed and dated curriculum vitae of the principal investigator including a copy of the principal investigator's current medical license (required in the US) or medical registration number on the curriculum vitae
- A signed and dated Clinical Trial Agreement (CTA)
- A copy of the regulatory authority approval for the country in which the study is being conducted (if required), and the Import License (if required)

The investigator and the study staff (or if regionally required, the head of the medical institution or the designated pharmacist) will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, and (e) documentation of returns to the sponsor. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Regulatory Agency). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator (or if regionally required, the head of the medical institution or the designated pharmacist) by the subject and, together with unused study drugs that were shipped to the site but not dispensed to subjects, are to be returned to the sponsor's designated central or local depot(s) during the study or at the conclusion of the study, unless provision is made by the sponsor for destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depot(s). Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depot(s) must be boxed, sealed, and shipped back to the central or local depot(s) following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 Study Assessments

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, race/ethnicity, native language, handedness, and highest education level.

9.5.1.2 Baseline Assessments

9.5.1.2.1 MEDICAL HISTORY AND PHYSICAL EXAMINATIONS

Medical and surgical history, prior and concurrent medications including AChEI and memantine use, and current medical conditions will be recorded at the Screening Visit. All medical and surgical history within 10 years must be noted in the Medical History and Current Medical Conditions eCRF. Medical history will include history of cognitive impairment. Subjects will be asked about history of infections due to varicella zoster virus (chickenpox and herpes zoster/shingles) and HSV types 1 and 2 (orolabial herpes/cold sores and genital herpes, respectively). The medical history of such infections will include last outbreak, duration, relapse frequency, and severity. Subjects will also be asked about their vaccination history including vaccinations against varicella zoster virus and TB. The modified Hachinski ischemic score will be used to differentiate vascular dementia from dementia of Alzheimer's type.

Physical examinations will be performed as designated in Table 2 and Table 3. A complete physical examination will include evaluations of the head, eyes, ears, nose, throat, neck, chest (including heart and lungs), abdomen, limbs, a dermatologic exam, and a neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and sensory system). A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions eCRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the AEs eCRF.

The CDR, MMSE, FAQ, and ADAS-cog$_{14}$ are well-established clinical tools for use in the assessment of AD.

9.5.1.3 Efficacy Assessments

9.5.1.3.1 PSYCHOMETRIC ASSESSMENTS

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and a study partner who knows and has contact with the subject. The CDR is a clinician-directed assessment of both cognition and function, and is intended to capture the state and therefore the disease stage of the individual. The CDR has been proposed as an acceptable approach for following disease progression and confirming treatment in AD.

The CDR assesses 6 domains of subject function: memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. Each of these items has a maximum possible score of 3 points and the total score is a sum of the item scores (sum of boxes) giving a total possible score of 0 to 18 with higher scores indicating more impairment.

ISLT: The ISLT is a verbal learning and episodic memory test assessing both immediate and delayed recall. Subjects are read a list of 12 items that can be obtained at the local shopping center. Subjects are asked to recall as many of the items as possible and this immediate recall trial is repeated 3 times. After a delay of approximately 20 to 30 minutes, in which time the CBB will be performed as a distractor task, subjects are again asked to recall as many of the words on the shopping list as they can (ie, a delayed recall trial).

MMSE: A 30-point scale that measures orientation to time and place, registration, immediate and delayed recall, attention, language, and drawing. Scores range from 0 (most impaired) to 30 (no impairment).

ADAS-cog$_{14}$: The ADAS-Cog is the most widely used cognitive scale in AD clinical studies (Rosen, et al., 1984). The 14-item version will be used in the present study since it is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects (Fleisher, et al., 2007). The Word List Learning Immediate and Delayed Recall tasks from the ADAS-Cog$_{14}$ that will be used as secondary endpoints, employ methods that are similar to those used by the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al, 1989), (cited by Mohs et al, 1997). For this task, 10 words, each printed in large letters on 1 card, are shown one at a time for 2 seconds each. The subject is instructed to read the words aloud. Immediately after reading the list, the subject is asked to recall the list aloud. This procedure is repeated 3 times and the immediate memory score is the total number of words recalled during all 3 trials. The total number of words recalled ranges from 0-30. This task is given at the beginning of the ADAS-Cog$_{14}$. At the end of the ADAS-Cog$_{14}$, the subject is asked to recall as many words as possible from the previously studied list. The total number of words recalled on this Delayed Recall task ranges from 0-10.

FAQ: The study partner provides performance ratings (from 0 to 3) on 10 complex activities of daily living performed within the preceding 4 weeks. Scores range from 0 (independent) to 30 (dependent).

Audio recordings will be made during the administration of a number of the scales above for possible central review (as permitted by local regulations).

9.5.1.3.2 vMRI AND fMRI

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

vMRI sequences will be collected for all subjects immediately following all safety MRI scans in the same imaging session. vMRI will be conducted at either 1.5T or 3T, and across multiple scanner types and the type of scanner used will be documented. vMRI analysis will be performed by a central imaging laboratory on MRI scans obtained at the times specified in

Table 2 and Table 3, according to standard quality control and normalization procedures for measurements of the whole brain and total ventricular volume. Measurements of the right and left hippocampal volumes will be based on a validated algorithm and conducted in the same laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

Task free fMRI can be used to assess the integrity of functional networks within the brain to help determine effects of disease on brain function. The additional sequence will be collected on all subjects who can keep their eyes open (to control for occipital input) and stay awake. Any subject who cannot fulfill this set of instructions for 7-10 minutes at the end of the vMRI scan will not be included in this exploratory study.

fMRI data will be used to generate connectivity maps based on critical anatomical regions, (eg, precuneus, inferior frontal sulcus) which can then be used within subject to determine the effect of E2609 on preserving connectivity known to degrade with progression of AD.

Descriptions and detailed instructions for all imaging can be found in the MRI imaging manual that will be provided to the study MRI imaging facilities.

9.5.1.3.3 CEREBROSPINAL FLUID SAMPLING

Amyloid CSF is 1 of the 2 methods required at screening to determine subject eligibility for the study. Subjects that undergo the eligibility CSF sample collection or who consent to the CSF longitudinal substudy will be encouraged to stay at the site after completion of LP for medical observation. CSF sample(s) will be collected by LP (gravity drip method only) after fasting (preferred), or at least 2 hours after the most recent meal. Further guidance for the timing of CSF collection is provided in Section 9.5.1.4.2

Subjects who provide a CSF sample at Screening for amyloid eligibility purposes, but did not initially consent to the CSF longitudinal substudy may provide consent to the CSF longitudinal substudy at any point in time up to Visit 13 (or ED). INR testing should be performed for subjects who consent to provide a CSF sample and who have a medical condition with bleeding risk that is not under adequate control.

9.5.1.4 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Assessments

9.5.1.4.1 PHARMACOKINETIC ASSESSMENTS

Blood samples will be collected for the determination of the concentrations of E2609 in all randomized subjects. Analyses of metabolite concentrations may be performed, depending on emerging data from other studies with E2609.

Samples from all subjects receiving active treatment will be analyzed. In addition, a predetermined percentage of placebo samples will be analyzed. Remaining placebo samples will be held in storage in the event that further confirmatory analysis is requested. Plasma concentrations of analytes will be quantified by liquid chromatography with tandem mass spectrometry methodology using a previously validated assay.

Blood samples will be collected as specified in Table 2 and Table 3. Two plasma PK samples will be obtained at each of the following visits: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

Blood will also be drawn where possible at the first report of an SAE or severe unexpected AE and at its resolution.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures for PK samples.

9.5.1.4.2 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER, ASSESSMENTS

Biomarkers

The CSF sample will be used for PD assessments including but not limited to CSF Aβ(1-x), Aβ(1-42), Aβ(1-40), t-tau, p-tau, and BACE1 levels and activity.

The plasma sample will be used for Aβ(1-x) analysis and may be used for exploratory biomarker analyses. Aβ(1-x) in both CSF and plasma will be measured using a modified commercially available enzyme-linked immunosorbent assay (ELISA). The prescreening and postscreening analysis of CSF Aβ(1-42), Aβ(1-40), t-tau, and p-tau will be performed using commercially available ELISAs. BACE1 levels will be measured using internally developed fluorescence resonance energy transfer and ELISA based assay(s). Substrates of BACE1 inhibition may also be explored using Western blots or other amenable methodology if clinical observations warrant and if analytes can be reliably tested in samples collected.

Blood samples will be collected for PD assessments as specified in Table 2 and Table 3. The blood sample collected for PD analyses at Screening should be collected at fasting or at least 2 hours after the most recent meal and PD blood samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED) and, as far as is feasible, samples should be taken at the same time of day

Blood samples and CSF (if applicable) collected at Screening will be stored for determination of prior exposure to any suspected infective agents in the event that the subject develops TEAEs that warrant further investigation (eg, treatment-emergent infection). Testing may include, but not be limited to, serological tests (eg, HSV1 and 2), viral titer by

quantitative polymerase chain reaction (Q-PCR), and/or human leukocyte antigen (HLA) genotyping.

For all subjects, baseline and on-study blood samples, DNA samples, and any collected CSF samples (if applicable) will be stored for up to 15 years.

See the laboratory manual (to be supplied to study sites) for a description of the collection, handling, and shipping procedures of the biomarker samples.

Pharmacogenomics

A blood sample will be obtained at Screening and will be used to determine the *ApoE* genotype of subjects enrolled in this study. The findings will be used in the statistical analysis to determine the effects on treatment response and safety.

The genomic DNA samples will be stored and may also be used to examine the role of genetic variability in subjects' absorption, distribution, metabolism, and excretion, the development of AEs, or underlying AD. Variations in E2609 exposure or the occurrence of AEs observed in the study population may be evaluated by correlation of single–nucleotide polymorphisms with PK, safety, or PD data.

Details of PGx testing may be provided and reported separately.

Amyloid PET

An amyloid PET scan may be performed at Screening to confirm deposition of amyloid in the brain. A historical amyloid positive PET scan may be used if conducted within 12 months before the planned date of randomization and provided that the scan and result are considered acceptable by the central PET reading group. As part of an optional substudy, longitudinal amyloid PET imaging will also be conducted after 12 and 24 months of treatment (or at ED, provided the subject has received at least 39 weeks of study drug). Longitudinal amyloid PET imaging will only be conducted on subjects that have consented to this optional substudy and who have had Screening PET scans performed for this study (ie, historical scans cannot be used for the longitudinal analyses).

Descriptions and detailed instructions for all amyloid PET imaging can be found in the PET imaging manual provided to the study PET imaging facilities.

Further details regarding pharmacodynamics, pharmacogenomics, and other biomarker research is provided in Appendix 4.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and ECGs recordings evaluated by a central reader; physical, dermatologic and neurologic examinations; assessment of suicidality (using the C-SSRS or the clinical

assessment of suicidality as outlined in Table 2 and Table 3); and MRIs as detailed in Table 2 and Table 3. Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events. Blood samples for immunologic assessments will be collected as outlined in Table 2 and Table 3. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for testing. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

9.5.1.5.1 ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is E2609.

The criteria for identifying AEs in this study are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product (Note: Every sign or symptom should not be listed as a separate AE if the applicable disease [diagnosis] is being reported as an AE)
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, withdrawal of study drug, or withholding of study drug, whether prescribed in the protocol or not.

All AEs observed during the study will be reported on the eCRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the last visit (Visit 15, as shown in Table 3). Subjects who fail screening primarily due to AE(s) must have the AE(s) leading to screen failure reported on the Screening Disposition eCRF and the Adverse Event eCRF. SAEs will be collected for 12 weeks after the last dose.

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event eCRF.

Abnormal ECG (QTc) results, if not otherwise considered part of a clinical symptom that is being reported as an AE, should be considered an AE if the QTc interval is more than 450 ms and there is an increase of more than 60 ms from baseline. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. Any ECG abnormality that the investigator considers as an AE should be reported as such.

Cognitive decline will be assessed as a safety assessment in addition to an efficacy assessment. Cognitive assessments include the CDR, ADAS-cog$_{14}$, and MMSE (see Section 9.5.1.3.1). If these assessments show cognitive decline during the Treatment Period, and if this cognitive decline is considered by the investigator to be excessive relative to the subject's recent AD history, this finding should be reported as an AE. It is the responsibility of the investigator to review the cognitive assessments and to determine if any result constitutes an AE.

AEs that might indicate signals of possible drug abuse potential will require a more detailed follow-up through completion of a specific eCRF form. This includes AEs that fall into the following categories and examples of such AEs are provided in Appendix 3.

- Euphoric mood
- Elevated mood
- Feeling abnormal
- Feeling drunk
- Feeling of relaxation
- Thinking abnormal
- Hallucination
- Inappropriate affect
- Mood disorders and disturbances
- Drug tolerance
- Psychosis
- Dissociative state

It is also the responsibility of the investigator to review the results of the C-SSRS/clinical assessment of suicidality in all subjects and determine if any result constitutes an AE. Medical and scientific judgment should be exercised in deciding whether an isolated

suicidality rating scale response should be classified as an AE (see Section 9.5.1.5.9 for a description of the C-SSRS and of the clinical assessment of suicidality).

The following adverse events will require the collection of information sufficient to provide a detailed description of the event, treatment, and outcome to the Medical Monitor for the study: any treatment-emergent significant laboratory abnormality; any seizures, herpes zoster infection, severe infection; any moderate to severe drug rash or any rash lasting more than 72 hours (regardless of severity); amyloid-related imaging abnormalities (cerebral vasogenic edema, macrohemorrhage, an area of superficial siderosis, or a new microhemorrhage); a positive suicidality assessment on either the C-SSRS or the clinical assessment of suicidality

All AEs must be followed for 12 weeks after the subject's last dose, or until resolution, whichever comes first. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have absolute lymphocyte count measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

Assessing Severity of AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the eCRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see Section 9.5.1.5.2 for the definition of an SAE).

Assessing Relationship to Study Treatment

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event

- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

Classification of Causality

The relationship of each AE to the study drug will be recorded on the eCRF in response to the following question:

Is there a reasonable possibility that the study drug caused the AE?

Yes (related) A causal relationship between the study drug and the AE is a reasonable possibility.

No (not related) A causal relationship between the study drug and the AE is not a reasonable possibility.

9.5.1.5.2 SERIOUS ADVERSE EVENTS AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the adverse event as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

For this study, the following events should always be considered serious and reported as an important medical event even if it does not meet other serious criteria:

- Ocular herpes
- New onset seizures
- Symptomatic cerebral vasogenic edema

In addition to the above, events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose,

misuse, abuse, or medication error. These events associated with special situations are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs.

All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization.

The following hospitalizations are not considered to be SAEs because there is no "adverse event" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care
- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed after study drug administration)
- Hospitalization for administration of study drug or insertion of access for administration of study drug
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

If possible, a blood sample for the measurement of study drug plasma concentration should be drawn at the first report of an SAE or a severe unexpected AE and at its resolution.

9.5.1.5.3 LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, urinalysis, and CSF are summarized in Table 1. Subjects should be in a seated or supine position during blood collection. Table 2 and Table 3 show the visits and time points at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 1 Clinical Laboratory Tests

Category	Parameters
Hematology	Hematocrit, hemoglobin, platelets, red blood cell count, and white blood cell count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	Bicarbonate, calcium, chloride, phosphate, potassium, sodium
Liver function tests	Alanine aminotransferase, alkaline phosphatase, aspartate aminotransferase, gamma glutamyl transpeptidase, direct bilirubin, total bilirubin
Renal function tests	Blood urea/blood urea nitrogen, creatinine
Other	Albumin, cholesterol, globulin, glucose, lactate dehydrogenase, total protein, triglycerides, uric acid
Urinalysis	Bacteria, casts, crystals, epithelial cells, glucose, ketones, occult blood, pH, protein, red blood cells, specific gravity, white blood cells Urinalysis (sent to a central lab at Screening; assessed via dipstick at site during randomization phase)
Other	Viral screen (HCVAb [Hepatitis C] and HBsAg [Hepatitis B]). Viral characterization (HSV-1, HSV-2, and CMV) Serum pregnancy test (at Screening, females of child-bearing potential only) Urine pregnancy test (assessed via a dipstick at site during randomization phase, females of child-bearing potential only) Tests for thyroid function and vitamin B12 Blood samples for immunologic assessments. Some of the immunologic assessment blood sample will be used to prepare isolated PBMCs which will be stored for later testing. Cerebrospinal fluid sampling NOTE: INR testing should be performed for subjects who consent to provide a CSF sample and who have a medical condition with bleeding risk that is not under adequate control.

CMV = cytomegalovirus, CSF = cerbreospinal fluid, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HSV-1 = herpes simplex virus-1, HSV-2 = herpes simplex virus-2, INR = International Normalized Ratio, PBMC = peripheral blood mononuclear cell

Clinical laboratory tests during all phases of the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory. Laboratory certification as available will be included in the final clinical study report for this study.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see Section 9.5.1.5.1 and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event eCRF.

9.5.1.5.4 VITAL SIGNS AND WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], heart rate [beats per minute (bpm)], respiratory rate [per minute], body temperature [in centigrade]), and weight (kg) will be obtained at the visits designated in Table 2 and Table 3 by a validated method. Measurements of BP and heart rate will be obtained with the patient in a sitting position. All BP measurements should be performed on the same arm, preferably by the same person.

9.5.1.5.5 PHYSICAL EXAMINATIONS

A complete physical examination with dermatologic review and a full neurologic exam including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system will be conducted at Screening as described in Section 9.5.1.2.1. At Visit 2 and during the Randomization Phase, routine physical examinations (including dermatologic review) will take place as shown in Table 3. These examinations will include the assessment of the cardiovascular system, respiratory system, and neurologic system. Health status will be evaluated by brief evaluation of the eyes, ears, nose, throat, and other physical conditions of note. The subject must be queried regarding changes in physical status since the last examination. A urogenital examination will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Only changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events eCRF.

Dermatologic Assessment

A dermatologic assessment will be performed as part of the routine physical examination at the times shown in Table 2 and Table 3. These examinations will specifically include evaluation of any areas of depigmentation, drug-induced vitiligo, or any rash.

In addition subjects will be questioned by the investigator at each visit about any new lesions on the skin, orolabial area, genital area, mucous membranes and conjunctiva, or visually detectable changes that might represent a drug-induced rash/reaction or infection. Subjects and their study partners will be instructed to contact the investigator promptly if they see any lesions or other symptoms that might be associated with a drug-induced rash or reaction, or infection, and the investigator will be required to review such AEs as soon as possible and consider an UNS physical and dermatologic evaluation. Detailed characteristics of any skin rashes will be captured in the eCRF as either medical history or AEs. Treatment-emergent abnormal dermatologic findings should be reported as AEs.

A subject with any skin rash of moderate to severe intensity, or any rash lasting more than 72 hours regardless of severity (with the exception of oral or genital herpes as described in the next paragraph), will be discontinued from study drug and a dermatologic consult will be requested regardless of whether the rash is considered drug related or due to other causes. For cases where the investigator suspects a drug rash, regardless of severity, the subject will be discontinued from study drug, a dermatologic consult will be requested, and a skin biopsy

will be performed to confirm the diagnosis. The skin rash will be treated as per standard care and will be followed up until resolution regardless of etiology or severity.

Subjects who develop moderate to severe oral or genital herpes should be discontinued from study drug. Subjects who develop a mild case of oral or genital herpes may remain on study drug even if the event lasts more than 72 hours.

Neurologic Examination

A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Screening and at Visit 13 (or ED). During the randomization phase, neurologic examinations will be performed at regular intervals as shown in Table 3 and will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history. Treatment-emergent abnormal neurologic findings should be reported as AEs.

9.5.1.5.6 ELECTROCARDIOGRAMS

Electrocardiograms will be obtained as designated in Table 2 and Table 3. A single 12-lead ECG will be recorded after subjects have been resting in the supine position for at least 5 minutes. If the QTcF is greater than 450 ms on the first single 12-lead ECG, 2 additional 12-lead ECGs will be performed 1 minute apart and the mean of the 3 QTcF values will be calculated. All ECG recordings will be evaluated by a central reader.

On any study day when ECG, vital signs, and blood samples are taken, it is recommended that these procedures should be conducted in the following order: ECG first, followed by vital signs, and then blood samples.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 9.5.1.5.1) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the AEs eCRF.

9.5.1.5.7 MRI (INCLUDING VMRI AND FMRI)

Brain MRI assessments, including vMRI and fMRI, will be performed at the times shown in Table 2 and Table 3. Additional safety MRI scans can be performed at UNS visits if clinically necessary. MRI acquisition and interpretation will be organized centrally to ensure reproducibility and consistency between units involved.

MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9, and 13. In the event of an UNS Visit, the investigator in consultation with the sponsor will determine whether or not an additional

safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days. A vMRI sequence will be collected in all subjects immediately following all scheduled MRI assessments.

9.5.1.5.8 PREGNANCY TEST

At Screening, females of childbearing potential will have a serum pregnancy test. At Visit 2 and during the Treatment Phase, urine samples will be obtained from females of childbearing potential for dipstick pregnancy tests (see Table 3).

9.5.1.5.9 ASSESSMENT OF SUICIDAL THINKING AND BEHAVIOR

An assessment of suicidal thinking and behavior will be performed at every visit; the C-SSRS will be performed at Screening, Visit 2, and at the end of treatment time points as shown in Table 2 and Table 3, with a more general clinical assessment by the investigator, involving both the subject and the study partner, at all other visits. A positive suicidality assessment on the clinical assessment of suicidality will trigger a C-SSRS to be administered. A positive suicidality assessment on the C-SSRS will trigger additional psychiatric evaluations by a psychiatrist to determine how the subject is to be managed clinically. All sites are required to identify a psychiatrist for referral purposes. The subject's ability to continue to participate in the study will be determined by the investigator in consultation with the Medical Monitor.

9.5.1.5.10 BIOMARKERS SAMPLES

As noted in Section 9.5.1.4.2, CSF, blood, and DNA samples will be collected and may be tested in the event that a subject develops AEs that warrant further investigation.

9.5.1.6 Other Assessments

The NPI-10 item will be conducted at Visit 2 and then every 6 months. HRQoL will be measured using EQ-5D and QOL-AD at screening and every 6 months following randomization. In order to confirm the validity of the answers provided by the subject, the study partner will serve as subject's proxy and complete the EQ-5D and QOL-AD to rate the subject's HRQoL. In addition, the study partner will complete (self-report) their own EQ-5D. As a result, a set of 3 EQ-5Ds (1 from the subject; 2 from the study partner) and 2 QOL-ADs (1 from the subject; 1 from the study partner) will be provided at each visit. Additionally, the primary study partner burden will be measured using Zarit's Burden Interview every 6 months to assess the stresses experienced by study partners.

At visits where the EQ-5D, QOL-AD, or Zarit's Burden Interview are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject amongst other factors.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 2 presents the schedule of procedures/assessments for the Prerandomization Phase (see below).

Table 3 presents the schedule of procedures/assessments for the Randomization Phase.

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

Phase	**Prerandomization**
Period	**Screening**
Visit	**1**
Procedures/ Assessments (to be completed in a maximum of 50 days, plus an additional window of up to 30 days if required)	
Inclusion and exclusion criteria	X (All tiers)
Prior / concomitant meds including AD meds	X (All tiers)
Adverse events	X (All tiers)
Informed consent (subject and study partner)	X (Tier 1)
Optional subject informed consent to CSF and PET substudies[a]	X (Tier 1)
Demographics	X (Tier 1)
Medical history (including cognitive impairment history)	X (Tier 1)
Clinical diagnosis and disease staging[b]	X (Tier 1)
MMSE[c]	X (Tier 1)
ISLT total recall, CBB, and ISLT delayed recall[c]	X (Tier 1)
CDR[c]	X (Tier 1)
Modified Hachinski ischemic scale	X (Tier 1)
EQ-5D[d]	X (Tier 2)
QOL-AD[e]	X (Tier 2)
Zarit's Burden Interview of study partner	X (Tier 2)
C-SSRS	X (Tier 2)
Complete physical exam including dermatologic review	X (Tier 3)
Full neurologic examination	X (Tier 3)
Vital signs[f]	X (Tier 3)
Height, weight, and BMI	X (Tier 3)
Single 12-lead ECG[g]	X (Tier 3)
Blood samples for clinical chemistry, hematology, thyroid function, vitamin B12[h]	X (Tier 3)
Blood samples for PG[i]	X (Tier 3)
Blood samples for PD and exploratory biomarkers[j]	X (Tier 3)
Blood sample for immunologic assessments, including isolation of PBMCs for storage and later testing	X (Tier 3)
Blood for viral screen[k]	X (Tier 3)
Serum pregnancy test[l]	X (Tier 3)
Urinalysis (central lab)	X (Tier 3)
MRI including vMRI and fMRI (for PD)[m]	X (Tier 4)
Amyloid PET (for eligibility and longitudinal PET baseline)[n]	X (Tier 5)
CSF sampling (for eligibility and PD baseline)[n,o,p]	X (Tier 5)

NOTES:

Table 2 Schedule of Procedures/Assessments in Study E2609-G000-302: Prerandomization Phase

- Screening assessments/procedures have been organized into 5 distinct tiers. All assessments and procedures in each tier should be completed, and eligibility to continue confirmed, before any assessments/procedures from the next tier commence. Tier 2 and Tier 3 procedures may be performed on the same day as Tier 1 procedures, as long as the results of the procedures from the earlier Tier(s) show that the subject is eligible to continue with screening activities.
- All screening assessments are to be completed within 50 days, plus an additional window of up to 30 days if required. Visit 2 (Randomization) should occur as soon as possible after completion of all Screening assessments/procedures and confirmation of eligibility to continue in the study, and no more than 10 days after completion of the last screening assessment (amyloid eligibility assessment).

AD = Alzheimer's disease, ApoE = apolipoprotein E, BMI = body mass index, CBB = Cogstate Brief Battery, CDR = Clinical Dementia Rating, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, EQ-5D = EuroQol-5 Dimensions, fMRI = functional MRI (to be performed task free at resting state), INR = International Normalized Ratio, ISLT = International Shopping List Task, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamic, PET = positron emission tomography, PG = pharmacogenomic, PK = pharmacokinetic, QTc = corrected QT interval, QOL-AD = Quality of Life in Alzheimer's Disease, vMRI = volumetric MRI.

a: Subjects should be informed about the optional CSF and PET longitudinal substudies as part of Tier 1 of the Screening Visit. However, subjects are able to consent to 1 or both substudies at any time up to Tier 5 of the Screening Visit. Furthermore, subjects who have an amyloid PET for eligibility (Tier 5) may consent to the PET substudy after Tier 5, ie during the Randomization Phase of the study. Similarly, subjects who provide a CSF sample for eligibility (Tier 5) may consent to the CSF substudy after Tier 5 (ie during the Randomization Phase of the study).

b: The diagnosis and clinical disease staging will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

c: It is recommended that the MMSE and ISLT be completed, and eligibility on these assessments be confirmed, prior to the CDR being completed. Subjects will be diagnosed with either MCI due to AD or the early stages of mild AD as defined by the protocol after completion of the MMSE, ISLT, and CDR. The Cogstate Brief Battery (CBB) will be administered in the 20 to 30 minutes between the ISLT total recall and delayed recall tests. Subjects will also be evaluated on the modified Hachinski ischemia scale. Subjects who are considered ineligible for this study based on these assessments should not continue with the rest of the assessments for the Screening visit.

d: There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

e: There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject using the study partner

f: Measurements of body temperature, sitting blood pressure and sitting heart rate will be obtained.

g: Single 12-lead ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values

h: Thyroid function tests include thyroid stimulating hormone, free triiodothyronine, and free thyroxine.

i: For subjects who are approved for rescreening, pharmacogenomic testing need not be repeated if a sample was collected, processed, and *ApoE4* results issued during the previous screening procedure. Great care must be taken to link the *ApoE* status information with the new subject number.

j: The blood samples taken for PD and exploratory biomarkers should be collected at fasting or at least 2 hours after the most recent meal. For subjects who are going to provide a CSF sample at Tier 5 for amyloid eligibility and/or PD baseline purposes, the timing of the blood draw for PD and exploratory biomarkers should be at approximately the same time of day as planned for the LP.

k: Viral screen to include HCVAb (Hepatitis C) and HBsAg (Hepatitis B).

l: Only required for female subjects of childbearing potential

m: For subjects who are approved for rescreening, MRI and vMRI need not be repeated if the date of the rescreen is no more than 90 days from the date of the original screening MRI.

n: PET scanning will be performed with a locally approved amyloid imaging agent (eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally); for subjects participating in the PET substudy, the imaging agent must remain unchanged throughout the study. CSF collection should always precede amyloid PET, and the 2 assessments should be separated by at least 24 hours. A positive amyloid result is needed for only 1 of the 2 amyloid eligibility procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the amyloid PET need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. If a rescreened subject will participate in the longitudinal PET substudy, quantitative PET collection should be repeated if the original PET collection was done greater than 6 months from the date of the original screening procedure

o: For those subjects who consent to the longitudinal CSF substudy, CSF should be collected at the same time of day for each assessment, preferably fasting or at least 4 to 8 hours post meal. For those subjects who consent to CSF and PET eligibility assessments, CSF collection should always precede amyloid PET, and the 2 assessments should be separated by at least 24 hours. For these subjects, a positive amyloid result is needed for only 1 of the procedures to confirm eligibility (ie, even if 1 of the 2 results is negative for amyloid, the subject would still be eligible under the other, positive result). For subjects who are approved for rescreening, the CSF need not be repeated for eligibility if confirmed amyloid positive during the original screening procedure. A gravity drip collection method must be used. Subjects will be encouraged to stay at the site after completion of LP for medical observation.

p: Subjects with a medical condition with bleeding risk that is not under adequate control (including a platelet count <50,000 or INR >3) are excluded from CSF collection.

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Routine physical examination with dermatologic review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Inclusion and Exclusion criteria	X															
Vital signs and respiratory rate[f]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Weight	X				X	X	X	X	X	X	X	X	X		X	X
Neurologic examination[g]					X	X		X		X		X	X		X	X
Concomitant medications[h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Single 12-lead ECG[i]	X		X		X	X		X		X		X	X	X	X[e]	X
Blood samples for clinical chemistry and hematology	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine sample for dipstick urinalysis[j]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[e]	X
Blood sample for immunological assessments, including isolation of PBMCs for storage and later testing	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Urine pregnancy test (females of CBP only)[k]	X		X	X	X	X	X	X	X	X	X	X	X	X		X
Blood sample for viral characterization[l]	X															
Blood sample for storage for immune status[m]	X		X		X	X		X				X	X	X	X	X
MMSE[n]	X					X		X		X		X	X	X	X	
CDR[n]	X				X	X	X	X	X	X	X	X	X	X	X	

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
ADAS-cog$_{14}$[n]	X					X		X		X		X	X	X	X	
FAQ[n]	X					X		X		X		X	X	X	X	
Disease Staging[o]					X	X	X	X	X	X	X	X	X		X	
NPI$_{10}$	X					X		X		X		X	X		X	
C-SSRS	X											X	X			
Clinical assessment of suicidal thinking and behavior[p]		X	X	X	X	X	X	X	X	X	X			X	X	X
EQ-5D[q]						X		X		X		X	X			
QOL-AD[r]						X		X		X		X	X			
Zarit's Burden Interview of study partner						X		X		X		X	X			
MRI including vMRI and fMRI[s]								X				X	X			
Amyloid PET (optional substudy)[t]								X				X	X			
Telephone contact[u]		X	X		X	X		X		X		X	X			
Blood samples for PK[v]		X	X		X	X		X		X		X	X			
Blood samples for PD and exploratory biomarkers[w]		X	X		X	X		X		X		X	X	X	X	
CSF sampling for PK and PD (optional substudy)[x]												X	X			
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 3 Schedule of Procedures/Assessments in Study E2609-G000-302

Phase	**Randomization**															
Period	**Treatment**													**Follow-Up**		
Visit[a]	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**ED**[b]	**14**[c]	**15**[c]	**UNS Visit**[d]
Day	**1**	**15**	**29**	**57**	**85**	**183**	**274**	**365**	**456**	**547**	**638**	**729**		**757**	**813**	
Week	**1**	**3**	**5**	**9**	**13**	**27**	**40**	**53**	**66**	**79**	**92**	**105**		**109**	**117**	
Weeks elapsed since 1st dose	**0**	**2**	**4**	**8**	**12**	**26**	**39**	**52**	**65**	**78**	**91**	**104**		**108**	**116**	
Nominal months elapsed since 1st dose	**0**		**1**	**2**	**3**	**6**	**9**	**12**	**15**	**18**	**21**	**24**		**25**	**27**	
Procedures/ Assessments																
Sleep/dream questionnaire[y]																X
Randomization	X															
Dispense study drug	X[z]	X	X	X	X	X	X	X	X	X	X					

Notes for Table 3

ADAS-cog$_{14}$ = Alzheimer's Disease Assessment Scale - Cognitive subscale (14 items), CBP = childbearing potential, CDR = Clinical Dementia Rating scale, CMV = cytomegalovirus, CNS = central nervous system, CSF = cerebrospinal fluid, C-SSRS = Columbia Suicide Severity Rating Scale, ECG = electrocardiogram, ED = Early Discontinuation, EQ-5D = EuroQol-5 Dimensions, FAQ = Functional Assessment Questionnaire (also known as the Functional Activities Questionnaire), fMRI = functional MRI (to be performed task free at resting state), HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), INR = International Normalized Ratio, LP = lumbar puncture, MMSE = Mini Mental State Examination, MRI = magnetic resonance imaging, NPI = Neuropsychiatric Inventory, PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PET = positron emission tomography, PK = pharmacokinetics, QOL-AD = Quality of Life in Alzheimer's Disease, UNS = unscheduled, vMRI = volumetric MRI.

[a] A window of ±3 days will be permitted for Visits 3 and 4. A window of ±7 days will be permitted for Visits 5 and 6. A window of ±10 days will be permitted for Visit 7 to 13 inclusive. A window of ±3 days will be permitted for the Follow-Up Visits. If use is made of the permitted visit windows, every effort should be made to bring the subject back in line with the "weeks elapsed since 1st dose" at subsequent visits.

[b] Subjects who discontinue taking study drug prematurely for any reason will undergo an ED Visit within 7 days of their last dose of study drug. In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively). Subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinue treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy (MMSE, CDR, ADAS- cog$_{14}$) and quality of life (EQ-5D, QOL-AD and Zarit's Burden Interview) will be assessed along with concomitant medications and AEs. These 12 and 24 month clinical assessment visits do not need to be attended if they fall within 8 days (visit window) after the ED Visit or within ±8 days of either of the Follow-Up Visits (Visit 14 and Visit 15).

[c] All subjects, regardless of whether they complete all 24 months of treatment or discontinue study drug prematurely, will complete 2 posttreatment Follow-Up Visits; one 4 weeks after the last dose of study drug and a second 12 weeks after the last dose of study drug (Visit 14 and Visit 15 respectively). If clinically indicated, more frequent safety assessments can be made as UNS assessments or visits during the posttreatment Follow-Up Period. Subjects who have a Grade 2 or greater lymphocytopenia (less than 800/mm^3) during the follow-up period (ie, at either Visit 14 or Visit 15) should have absolute lymphocyte count measured every 4 weeks until resolution or confirmation of a non drug-related cause of the lymphocytopenia.

[d] Unscheduled visits may be conducted at any time that additional assessments, including MRI scans, are clinically indicated in the judgment of the investigator. Note that not all assessments indicated under UNS Visits need be conducted – actual assessments needed will be determined by the investigator and will be based on the specific visit needs.

[e] Only if clinically significant abnormalities are found at Visit 14 and the investigator considers it necessary to repeat at Visit 15.

[f] Measurements of body temperature and sitting blood pressure and sitting heart rate will be obtained.

[g] A full neurologic examination (including general status, cranial nerve function, motor system, coordination/cerebellar function, reflexes, and, sensory system) will be performed at Visit 13 (or ED). Neurologic examinations at the other visits will focus on new symptoms and signs which will then alert the investigator to consider the occurrence of new CNS pathology. Examples of neurologic symptoms and signs that may indicate new CNS pathology that may need further investigation include (but are not limited to) visual disturbance, dysarthria, dysphasia, muscle strength, limb weakness, hyperflexia, paraparesis, micturition difficulty or urgency or incontinence, ataxia, neuropsychiatric or cognitive decline in excess of expectations based on the subject's recent history.

[h] Please refer to the Concomitant Drug/Therapy Section 9.4.7, which details prohibited and permitted medications in the study and associated time frames.

[i] Single 12-lead standard ECGs will be recorded. If the QTcF is greater than 450 ms, perform 2 more 12-lead standard ECGs 1 minute apart and take the mean of the 3 QTcF values.

[j] If dipstick urinalysis performed at site is abnormal, a urine sample will be sent to the central laboratory for full urinalysis.

[k] If urine dipstick pregnancy test is positive, a blood sample will be drawn for serum pregnancy testing by the central laboratory.

[l] Viral characterization will include testing for previous exposure to CMV, HSV1, HSV2, etc.

[m] Blood samples will be collected and stored. These samples may be used for exploratory biomarker analyses, or in the event that the subject develops treatment-emergent adverse events that warrant further investigation (eg, treatment-emergent infection), these samples may be tested to determine whether the subject already had prior exposure to any suspected infective agents.

[n] The subject components of these assessments are to be completed in the morning whenever possible, or consistently at the same time of day. Ideally, the subject component of these assessments

Notes for Table 3

should be completed before more invasive assessments or procedures (eg, physical examination, ECG, blood draws). The FAQ is to be administered to the study partner. At visits where the CDR or FAQ are conducted, the investigator will determine whether the study partner must attend in person or whether telephone contact will be suitable, and will base this determination upon the functional ability of the subject among other factors.

o Disease staging will be performed every 3 months. The site clinician is required to confirm the staging of disease, ie for subjects who were, at Screening, not clinically staged as dementia, does the subject still meet the definition of MCI due to AD or have they progressed into the stage of clinical dementia. This staging decision will be verified via a central review process and adjudicated if necessary. Adjudication will only occur when there is a discrepancy between the diagnosis and clinical disease staging made by the site compared to that determined by the central review process; moreover, where adjudication is required, it will be undertaken by an independent assessor(s).

p The clinical assessment of suicidality will require input from both the subject and the study partner

q There are 3 components to the EQ-5D as follows: (1) in the subject by self report, (2) in the study partner by self report, (3) in the subject by proxy using the study partner

r There are 2 components to the QOL-AD as follows: (1) in the subject by self report, (2) in the subject by proxy using the study partner

s MRI scans are to include vMRI and fMRI sequences and will be read by an approved central reader. MRI imaging will be conducted on separate days from the scheduled visits. MRI imaging should be conducted within the 7 days before Visits 9 and 13. In the event of an Unscheduled Visit, the investigator in consultation with the Medical Monitor will determine whether or not a safety MRI should be conducted. If an ED Visit takes place, an MRI is to be conducted if not already performed during the preceding 90 days.

t PET scanning (if subject has consented to optional substudy) will be performed with a locally approved amyloid β imaging agent, eg, Amyvid, if available or an agent under clinical investigation if no agents are approved locally; the imaging agent must remain unchanged for an individual subject throughout the study. A PET scan will only be performed at an ED Visit if the subject has been treated with study drug for at least 39 weeks.

u Site staff will contact the subject or the study partner the day before the PK blood sampling to provide instructions that subjects must not take their study drug at home on the day of the PK blood sampling. During this telephone contact with the subject or the study partner, the site staff should document the time that the subject took their study drug that day, ie, the day before the PK blood sampling.

v Two plasma PK samples will be obtained: 1 sample at predose (trough) and another sample 1 to 6 hours postdose at Visits 3, 4, 6, 7, 9, and 11 and another sample 4 to 8 hours postdose at Visit 13 (or ED). Therefore, subjects or their study partners must be instructed not to take their study drug at home on the day the PK sampling is performed. Instead, subjects will take the study drug at the clinic after collection of the predose PK sample. At Visit 13 (or ED) the PK blood sample should be collected shortly before or after completing the LP for subjects participating in the CSF substudy. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the trough PK sample will still be collected. For subjects participating in the CSF substudy who have stopped taking study drug prior to the ED visit, the LP should be performed at approximately the same time as at the Screening Visit, and then a trough PK sample will be collected either shortly before or shortly after the LP.

w PD and exploratory biomarker blood samples should be collected at fasting or at least 2 hours after the most recent meal and, as far as is feasible, samples should be taken at the same time of day at all visits. Samples should be taken predose at Visits 3, 4, 6, 7, 9, 11, and 13 (or ED).

x For subjects who consent to participate in the CSF longitudinal substudy. Visit 13 (or ED) also includes blood PK and PD assessments and so the subject will be dosed at the clinic on these days. A CSF sample will be collected by LP between 4 and 8 hours postdose and at the same time of day as the subject's Screening LP (±1 hour). The CSF sample will be taken with the subject fasting (preferred) or at least 2 hours after the most recent meal. A gravity drip collection method must be used. If performed on the same day as the cognitive tests, the LP will be performed after the cognitive tests; the subject should rest and drink some fluid to hydrate after the cognitive tests and before the LP. Subjects will be encouraged to stay at the site after completion of LP for medical observation. The CSF sample will not be taken at the ED Visit if this visit occurs within 3 months of a previous CSF sample. If at an ED Visit, the subject has already stopped study drug, then no dosing will take place, but the CSF sample will still be collected unless it was already collected within the past 3 months. Subjects with a medical condition with bleeding risk that is not under adequate control (including a platelet count < 50,000 or INR >3) are excluded from CSF collection.

y Subjects reporting AEs relating to abnormal dreams, nightmares, or sleep terror will be questioned on the nature, frequency, and impact of these events.

z The 1st dose of study drug will be given to the subject at the study site and the subject will be encouraged to stay at the site for an appropriate period of time for postdose medical observation.

9.5.2.2 Description of Procedures/Assessments Schedule

Please refer to Table 2 and Table 3 for the timings of the procedures and assessments to be performed during the study. Screening assessments will be organized into 5 tiers (see Table 2). See Section 9.5.1 for a full description of the procedures and assessments to be performed during this study.

Table 4 presents the number of blood and CSF samples, and the total volume of blood and CSF that will be collected throughout the study. Additional samples may be taken at the discretion of the investigator if the results of any tests fall outside reference ranges or if clinical symptoms necessitate testing to ensure subject safety.

Table 4 Summary of Blood and CSF Sample Volumes

Assessment	Total Number of Collection Time Points	Sample Volume, Number of Time Points x Volume per Collection (mL)		Total Volume (mL)
		Screening Visits	Treatment and Follow-Up Periods	
Blood				
Clinical chemistry	15	1×5 mL	14×5 mL	75 mL
Serum pregnancy test at Screening (females of childbearing potential only)	1	can use blood drawn for clinical chemistry	none	no additional volume
Hematology	15	1×2 mL	14×2 mL	30 mL
Thyroid function tests (thyroid stimulating hormone, free triiodothyronine and free thyroxine)	1	1×5 mL	None	5 mL
Viral screen at Screening (Hepatitis B and C)	1	1×5 mL	None	5 mL
Viral characterization at Visit 2 (previous exposure to CMV, HSV1, HSV2, etc.)	1	None	1 x 4 mL	4 mL
Vitamin B12 at Screening	1	1×5mL	None	5 mL
Blood for immunologic assessments, including isolation of PBMCs for storage and later testing	15	1×20 mL	14×20mL	300 mL
Blood for immune status	8	none	8×5 mL	40 mL
PD and exploratory biomarker sample	8	1×20 mL	7×12 mL	104 mL
PK analysis	8	1×4 mL	7×4 mL	32 mL
Pharmacogenomic sample	1	1×3 mL	None	3 mL
All blood samples, total volume collected		69 mL	534 mL	603 mL
CSF				
Amyloid eligibility	1	1×12 mL	none	12 mL
PD / PK (optional longitudinal substudy)	1	none	1×12 mL	12 mL

CMV = cytomegalovirus, CSF = cerebrospinal fluid, HSV1 = herpes simplex virus 1 (orolabial herpes), HSV2 = herpes simplex virus 2 (genital herpes), PBMC = peripheral blood mononuclear cell, PD = pharmacodynamics, PK = pharmacokinetic.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements commonly used in studies of AD.

Standard safety assessments incorporated into this protocol include assessment of AEs and SAEs, measurement of vital signs, clinical laboratory assessments, physical examinations (including dermatologic review), neurologic examinations, ECG measurements, assessments of suicidal thinking and behavior, and MRI.

9.5.4 Reporting of Serious Adverse Events, Pregnancy, and Events Associated with Special Situations

9.5.4.1 Reporting of Serious Adverse Events

All SAEs, regardless of their relationship to study treatment, must be reported on a completed SAE form by email or fax as soon as possible but no later than 24 hours from when the investigator becomes aware of the event.

SAEs, regardless of causality assessment, must be collected up to 12 weeks after the last dose of study drug. All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment or any protocol-required procedure should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report form be filled out as completely as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 1 business day of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE form.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor, or its designee, to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 28 days of last study treatment, or any exposure to study drug through breastfeeding during study treatment or within 28 days of last study treatment, must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported by fax or email as soon as possible but no later than 1 business day from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. The Pregnancy Report Form must be used for reporting. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 1 business day from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be withdrawn from study treatment.

9.5.4.3 Reporting of Events Associated with Special Situations

9.5.4.3.1 Reporting of Adverse Events Associated With Study Drug Overdose, Misuse, Abuse, or Medication Error

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject.

All AEs associated with overdose, misuse, abuse, or medication error should be captured on the Adverse Event eCRF and also reported using the procedures detailed in Reporting of

SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported using the SAE form and in an expedited manner but should be noted as nonserious on the SAE form and the Adverse Event eCRF.

9.5.4.3.2 Reporting of Study-Specific Events

Study-specific events (as detailed in Section 9.5.1.5.2 should always be considered as serious important medical events and be entered on the Adverse Event eCRF and reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet other serious criteria.

9.5.4.4 Expedited Reporting

The sponsor must inform investigators (or as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.5 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.6 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European Good Clinical Practice Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

A subject may elect to withdraw from the study at any time for any reason. All subjects who discontinue study drug early for any reason will undergo an ED Visit within 7 days of their last dose of study drug (see Section 9.1.2.2). In addition, Follow-Up Visits will be scheduled 4 and 12 weeks after the last dose of study drug (Visit 14 and Visit 15, respectively) (see

Section 9.1.2.2). These Follow-Up Visits will be conducted to monitor efficacy and safety parameters after early withdrawal from the study or discontinuation of study drug. See Table 3 for full details of the assessments to be performed at these visits.

All subjects who discontinue study drug before reaching 12 months of treatment will also be asked to return to the clinic for a 12 month clinical assessment and then again at 24 months. Subjects who discontinued treatment between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment. Subjects who discontinue early from study drug are considered "on study" as long as they continue to return for their clinical assessments at 12 and 24 months as outlined above, at which efficacy and quality of life will be assessed along with concomitant medications and AEs. However, subjects who discontinue study drug early are not considered to have 'completed' the study as a final Subject Disposition. A subject removed from the study for any reason may not be replaced.

The investigator will promptly explain to the subject involved that the study will be discontinued for that subject and provide appropriate medical treatment and other necessary measures for the subject. A subject who has ceased to return for visits will be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms.

The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.5.6 Abuse or Diversion of Study Drug

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5.1. Abuse is always to be captured as an AE.

During the study, the investigator should be aware of the possibility of abuse or diversion of study drugs and should report any concern about mishandling, abuse, loss, theft, or diversion of study drugs by completing the Abuse or Diversion of Study Drug eCRF.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he or she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 Data Quality Assurance

This study will be organized, performed, and reported in compliance with the protocol, standard operating procedure s, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the eCRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the eCRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the eCRF. The investigator or designee as identified on Form FDA 1572 (where applicable) must sign the completed eCRF to attest to its accuracy, authenticity, and completeness.

Completed, original eCRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both eCRF and external data (eg, laboratory data), will be entered into a clinical system.

Electronic source (eSource) methodology may be used for some of the clinical efficacy and HRQoL assessments performed in this study.

9.7 Statistical Methods

All statistical analyses will be performed by the sponsor or designee. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All statistical tests will be based on the 5% (2-sided) level of significance, unless specified.

9.7.1 Statistical and Analytical Plans

All statistical analyses will be performed by the Sponsor or designee after the study is completed and the database is locked and released for unblinding.

9.7.1.1 Study Endpoints

9.7.1.1.1 PRIMARY ENDPOINT

The primary endpoint of the study is:

- Change from baseline in the CDR-SB at 24 months.

9.7.1.1.2 SECONDARY ENDPOINTS

The secondary endpoints of the study are:

- Time to worsening of CDR scores by 24 months (eg, the worsening of global CDR score is defined as an increase from baseline by at least 0.5 points on the global CDR scale on 2 consecutive scheduled visits at which global CDR is undertaken)
- Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis
- The rate of change over time (mean slope) based on CDR-SB score over 24 months
- Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)
- Change from baseline in ADAS-cog$_{14}$, MMSE, and FAQ at 24 months
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months

9.7.1.1.3 EXPLORATORY ENDPOINTS

The exploratory endpoints of the study are:

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with AChEI or memantine after randomization) by 24 months
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months
- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

9.7.1.1.4 BIOMARKERS ENDPOINTS

The biomarker endpoints for this study are:

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

9.7.1.2 Definitions of Analysis Sets

- The Randomized Set is the group of subjects who are randomized to study drug.
- The Safety Analysis Set is the group of subjects who receive at least 1 dose of study drug and have at least 1 postdose safety assessment.
- The Full Analysis Set (FAS) is the group of randomized subjects who receive at least 1 dose of study drug and have baseline and at least 1 postdose primary efficacy measurement.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. The PP Analysis Set will be used to conduct a sensitivity analysis of the primary efficacy endpoint. Details of the evaluability criteria will be determined before database lock and treatment unblinding, and will be specified in the statistical analysis plan.
- The PK Analysis Set is the group of subjects with at least 1 quantifiable E2609 plasma concentration with a documented dosing history.
- The PD Analysis Set is the group of subjects who have sufficient PD data to derive at least 1 PD parameter.

9.7.1.3 Subject Disposition

The number of subjects screened, the number (percent) of subjects who failed screening, and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition eCRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other) will be presented.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation and secondary reason(s) for discontinuation, based on data reported on the Subject Disposition (Study Phase) CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who

completed the study, and discontinued from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, and other.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued from study drug will be summarized according to the primary reason for discontinuation and also according to secondary reason(s) for discontinuation, based on data reported on both the Subject Disposition (Study Phase) eCRF and ED from Study Drug eCRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study drug, and discontinued from study drug. The primary reasons for early discontinuation from the study drug are: AE, subject choice, pregnancy, inadequate therapeutic effect, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set and FAS will be summarized for each treatment group using descriptive statistics. Continuous demographic and baseline variables include age, CDR scores, ADAS-cog$_{14}$, MMSE and FAQ; categorical variables include sex, age group (equal or less than 65 years, age greater than 65 years), race, ethnicity, region, *ApoE4* genotype, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of mild AD).

9.7.1.5 Prior and Concomitant Therapy

All investigator terms for medications recorded in the eCRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD) (Mar 2014). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug. Concomitant medications will be defined as medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or (2) started on or after the date of the first dose of study drug up to the date of the last dose. All medications will be presented in subject data listings.

Medications taken within the 12-week Follow-Up Period will also be recorded.

9.7.1.6 Efficacy Analyses

The FAS will be used as the primary population for all efficacy analyses, while the PPS will be used as the supportive population.

9.7.1.6.1 PRIMARY EFFICACY ANALYSIS

The primary analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The primary analysis of the change from baseline in CDR-SB at 24 months will be performed to compare E2609 50 mg per day versus placebo using a linear mixed effects model for repeated measures (MMRM) on the FAS. The MMRM model will include baseline CDR-SB as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical dementia [yes, no], and concurrent AD medication use at randomization (Visit 2) [yes, no]), and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect; if MMRM fails to converge then a covariance structure with fewer parameters from the following list will be employed according to the prespecified order in the list until the MMRM converges. The list of covariance structure will include Heterogeneous Toeplitz, Toeplitz, Heterogeneous Compound Symmetry, and Compound Symmetry. This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The treatment effect for E2609 versus placebo will be compared at 24 months based on MMRM model. The LS means and difference in LS means between E2609 treatment group and placebo, and corresponding 95% CI will be presented.

The null hypothesis is that there is no difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo. The corresponding alternative hypothesis is that there is a difference in the mean change from baseline in CDR-SB at 24 months between E2609 50 mg per day and placebo.

The primary analysis will be repeated to minimize the impact of change in concomitant AD medications where efficacy data after initiation of new AD medications and increase of current AD medications will be censored.

The following sensitivity analysis will be conducted to evaluate the impact of missing data: the primary endpoint will be analyzed using ANCOVA after multiple imputation. The ANCOVA model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Subgroup analysis (eg, *ApoE4* genotype) and additional sensitivity analysis for the primary endpoint will be performed as appropriate.

9.7.1.6.2 SECONDARY EFFICACY ANALYSES

The secondary analyses will be performed only if the primary analysis is significant. The treatment effect for E2609 50 mg/day versus placebo, for each secondary efficacy endpoint, will be tested using a sequential testing procedure at a significance level of 2-sided alpha =0.05, ie., any test will start only if the test with higher hierarchical order is significant. The final hierarchical order will be specified later in the statistical analysis plan before database lock.

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Time

to worsening of a CDR score is defined as time from randomization to worsening of the CDR score (ie, the first worsening in 2 consecutive scheduled visits). For subjects whose CDR scores have not worsened by the end of study, the time to worsening of the CDR score will be censored at the date of last CDR assessment for these subjects.

Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis will be analyzed on the FAS using Cox regression model for treatment effect adjusting for randomization stratification factors. Proportion of subjects with dementia diagnosis at 24 months will be estimated using Kaplan—Meier method based on time to conversion to dementia based on clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis is defined as time from randomization to conversion to dementia based on clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia based on clinical diagnosis will be censored at the date of last dementia diagnosis.

The rate of change over time (mean slope) based on change from baseline in the CDR-SB will be analyzed using linear mixed effects (LME) models for multivariate normal data derived from a random coefficient model (slope analysis), where the mean slope in each group depends on a continuous assessment time. The LME model will include baseline CDR-SB, randomization stratification variables, assessment time, and treatment group-by-assessment time.

The other continuous secondary efficacy endpoints as defined above will be analyzed using the same MMRM model as the primary efficacy analysis to compare E2609 50 mg per day versus placebo on the FAS, using baseline value corresponding to the response variable in the model.

The relationship between clinical changes at 24 months (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in each of the biomarkers (amyloid PET, CSF t-tau and p-tau, vMRI, and fMRI) at 24 months, will be evaluated using an ANCOVA model. Changes in clinical scales at 24 months will be the response variables and either continuous or categorical change of biomarkers will be independent variables. The ANCOVA model will also include baseline value for clinical scale as a covariate, randomization stratification variables, treatment group as factors, and other terms as appropriate.

9.7.1.6.3 EXPLORATORY EFFICACY ANALYSES

Time to change of concomitant AD treatment will be analyzed similarly to that for time to conversion to dementia based on clinical diagnosis. Time to change of concomitant AD treatment is defined as time from randomization to the first dose increase and/or initiation of treatment with AChEI or memantine after randomization. For subjects without any change of concomitant AD treatment by the end of study, the time to change of concomitant AD treatment will be censored at the date of last assessment of concomitant medication.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly to that for proportion of subjects with dementia diagnosis at 24 months.

The rate of change over time (mean slope) based on change from baseline in the NPI-10 item will be analyzed in a manner similar to that used for the rate of change over time (mean slope) based on change from baseline in the CDR-SB.

The analysis of the following exploratory efficacy endpoints will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. For each exploratory efficacy endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in NPI-10 item at 24 months
- Change from baseline in EQ-5D (subject self-reported, study partner self-reported, and subject measured by proxy) and QOL-AD (subject and study partner) at 24 months
- Change from baseline in Zarit's Burden Interview at 24 months

Additional analyses may be performed as needed.

9.7.1.7 Pharmacokinetic, Pharmacodynamic, Pharmacogenomic, and Other Biomarker Analyses

9.7.1.7.1 PHARMACOKINETIC ANALYSES

Safety Analysis sets will be used for individual E2609 plasma and CSF concentration listings. The PK Analysis Set will be used for the summaries of E2609 plasma and CSF concentrations.

A population PK approach will be used to characterize the PK of E2609. The effect of covariates (ie, demographics) on E2609 PK will be evaluated. The PK model will be parameterized for clearance (CL) and volumes of distribution. Derived exposure parameters such as AUC will be calculated from the model using the individual posterior estimate of CL and dosing history.

9.7.1.7.2 PHARMACOKINETIC-PHARMACODYNAMIC

The PK/PD relationship between CSF biomarker levels and plasma PK parameters or CSF concentrations of E2609 will be explored graphically and any emergent relationship will be explored through population PK/PD modeling. These PK parameters include maximum observed concentration ($C_{max)}$, and $AUC_{(0\text{-}24)}$ derived from the population PK model. The PK/PD relationship between plasma PK parameters and CSF concentrations of E2609 with other biomarkers may also be explored using similar methods.

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of E2609 and CDR-SB at 24 months, and the relationship between various PK exposure parameters or CSF concentrations of E2609 and the change from Baseline for 24 months in ADAS-cog_{14}, and the MMSE, will be explored graphically. Any emergent relationships will be explored through population PK/PD modeling. The relationship between exposure to E2609 and most frequent AEs will also be explored.

9.7.1.7.3 PHARMACODYNAMIC, PHARMACOGENOMIC, AND OTHER BIOMARKER ANALYSES

The analysis of the biomarker endpoints defined as below will be performed to compare E2609 versus placebo using the appropriate prespecified statistical methods including MMRM model, analysis of covariance model (ANCOVA), etc. These analyses will be conducted without adjustment for multiplicity or sequential testing. For each endpoint, the treatment effect for E2609 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05.

- Change from baseline in amyloid PET SUVR composite at 24 months for brain amyloid levels
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Change from baseline in total hippocampal volume at 12 and 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI from predefined anatomical regions connectivity maps (eg, precuneus, inferior frontal sulcus)

The relationship between exposure (in CSF, plasma) of E2609 with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using appropriate statistical model with the continuous changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of E2609 as independent variables.

9.7.1.8 Safety Analyses

Evaluations of safety will be performed on the Safety Analysis Set. The incidence of AEs, out-of-normal-range laboratory safety test variables, abnormal ECG findings, and out-of-range vital signs, suicidality, results of the sleep questionnaire, along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

9.7.1.8.1 EXTENT OF EXPOSURE

The Duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment. The cumulative number and percent of subjects in each applicable exposure category will be presented by treatment group. Duration of exposure will be summarized using descriptive statistics as well as by 3-month duration categories using counts. The number and percent of subjects within each duration category will be presented by treatment group. Overall exposure (number of subject-months) is defined as summation over all subjects' exposure durations and will be summarized by treatment group.

9.7.1.8.2 ADVERSE EVENTS

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). AEs will be coded to the MedDRA (Version 19.0 or higher) lower level term

closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

A TEAE is defined as:

- An AE that emerges during treatment within 4 weeks of the last dose of study drug, having been absent at pretreatment (Baseline) or
- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that are treatment-emergent will be included in summary tables. All AEs, treatment-emergent or otherwise, will be presented in subject data listings.

The TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT. A subject will be counted only once within an SOC and PT, even if the subject experienced more than 1 TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes [related] and No [not related]).

The number (percentage) of subjects with treatment-related TEAEs will be summarized by SOC and PT. Treatment-related TEAEs include those events considered by the investigator to be related to study drug. The number (percentage) of subjects with treatment-related TEAEs will also be summarized by maximum severity (mild, moderate, or severe).

AEs will be summarized by the following subgroups: region, prior treatment with AChEIs or memantine (no or yes), and clinical subpopulation (MCI due to AD or the early stages of AD).

The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided. The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided. The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

9.7.1.8.3 LABORATORY VALUES

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters listed in Section 9.5.1.5.3, the actual value and the change

from baseline to each postbaseline visit and to the end of treatment (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in Section 9.5.1.5.3 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the end of treatment. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAVs). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a Grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a Grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

9.7.1.8.4 VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, systolic and diastolic BP, pulse, respiratory rate, temperature, weight), and changes from baseline will be presented by visit and treatment group.

9.7.1.8.5 OTHER SAFETY ANALYSES

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. Cognitive assessments will include the ADAS-cog_{14}, MMSE, and CDR. (see Section 9.7.1.6).

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy, including the change from Baseline in terms of the measured hippocampal volume based upon the centralized measurement of the structure on repeated MRIs. A large number of studies, including the AD Neuroimaging Initiative, have shown that quantitative measurements of hippocampal, whole brain, and total ventricular volume provide robust and reliable biomarkers of disease progression, and potential for assessment of PD efficacy.

MRI sequences will be collected for all subjects at 12 and 24 months per the Schedule of Assessments. vMRI data will be analyzed at the Screening Visit and at Visits 9 and 13 (12 and 24 months of treatment). QC and normalization procedures for measurements of the whole brain, total ventricular volume, and right and left hippocampal volumes will be based

on a validated algorithm and conducted in the same central laboratory. Additional analysis of regions of interest and cortical thickness may also be performed.

9.7.2 Determination of Sample Size

The sample size for this study is estimated based on comparison of E2609 versus placebo with respect to the primary efficacy endpoint, the change from baseline CDR-SB at 24 months. Based on available ADNI data [amyloid positive, MMSE equal or greater than 24, late MCI (global CDR=0.5) populations from ADNI, ADNI 2 and ADNI GO] the mean and the standard deviation of the change from baseline in the CDR-SB at 24 months in the placebo group are assumed to be 1.75 and 2.05, respectively. Therefore, assuming a 25% reduction in the mean change from baseline CDR-SB at 24 months for the E2609 50 mg per day dose group compared to placebo with a common standard deviation of 2.05 and an estimated 30% dropout rate in this study, a total sample size of 1330 subjects, 665 subjects in each treatment group, will be required to detect the treatment difference between E2609 50 mg per day and placebo using a 2-sample t-test with 90% power at a significance level of 2-sided alpha =0.05.

9.7.3 Interim Analysis

This is a fixed design. There is no interim analysis of efficacy and no alpha spending before final analysis. However, a futility analysis is planned when 30% subjects have completed 24 months. The sponsor may stop the trial for futility with nonbinding futility boundary calculated using conservative O'Brien-Fleming boundary of Lan-DeMets alpha spending function with 30% information based on completers. If the actual percent information of the futility analysis is different from 30%, the futility boundary will be recalculated using the actual percent information at time of futility analysis. A blinded sample size re-estimation through estimated standard deviation based on blinded data prior to the completion of enrollment, will be performed if there is an indication that sample size assumptions need to be changed. This blinded sample size re-estimation could be performed based on signals from external studies or based on review of blinded data from this study prior to completion of enrollment. The standard deviation of the primary endpoint was estimated based on data from the ADNI study. It is possible that the standard deviation for the same endpoint in clinical trials may be larger than that from this observation study.

An independent DSMB will convene at regular intervals to monitor the overall safety of the study and to make recommendations to the sponsor related to study safety as appropriate. The DSMB will be asked to review the cumulative safety data up to the date identified to make a determination if the trial is safe to proceed unchanged or to provide recommendations to the Sponsor as to how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. DSMB reviews will then continue to occur at regular intervals. Details will be provided in the DSMB Charter.

9.7.4 Other Statistical/Analytical Issues

Not applicable.

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the statistical analysis plan needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

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11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 Changes to the Protocol

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 Adherence to the Protocol

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 Monitoring Procedures

The sponsor's or CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site, and potential remote source document verification, will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The eCRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and to IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to, the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes that have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports (eg, sonograms, computed tomography scans, MRIs, radioactive images, ECGs, rhythm strips, electroencephalography, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dip-sticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source.

11.4 Recording of Data

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correct is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 Identification of Source Data

All data to be recorded on the eCRF must reflect the corresponding source documents, except when a section of the CRF itself is used as the source document.

11.6 Retention of Records

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of eCRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572, ICFs, and IRB/IEC correspondence). The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 Auditing Procedures and Inspection

In addition to routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's standard operating procedures to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 Handling of Study Drug

All study drug will be supplied to the principal investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA (or designated contractor).

11.9 Publication of Results

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed CTA between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study. The detailed obligations regarding the publication of any data, material results, or other information generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 Disclosure and Confidentiality

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or CTA executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 Discontinuation of Study

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 Subject Insurance and Indemnity

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 Sponsor's Grading for Laboratory Values

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	<LLN – 10.0 g/dL <LLN – 100 g/L <LLN – 6.2 mmol/L	<10.0 – 8.0 g/dL <100 – 80 g/L <6.2 – 4.9 mmol/L	<8.0 g/dL <80 g/L <4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	<LLN – 3.0×10^9/L <LLN – 3000/mm^3	<3.0 – 2.0×10^9/L <3000 – 2000/mm^3	<2.0 – 1.0×10^9/L <2000 – 1000/mm^3	<1.0×10^9/L <1000/mm^3
Lymphocytes	<LLN – 800/mm^3 <LLN – 0.8×10^9/L	<800 – 500/mm^3 <0.8 – 0.5×10^9/L	<500 – 200/mm^3 <0.5 – 0.2×10^9/L	<200/mm^3 <0.2×10^9/L
Neutrophils	<LLN – 1.5×10^9/L <LLN – 1500/mm^3	<1.5 – 1.0×10^9/L <1500 – 1000/mm^3	<1.0 – 0.5×10^9/L <1000 – 500/mm^3	<0.5×10^9/L <500/mm^3
Platelets	<LLN – 75.0×10^9/L <LLN – 75,000/mm^3	<75.0 – 50.0×10^9/L <75,000 – 50,000/mm^3	<50.0 – 25.0×10^9/L <50,000 – 25,000/mm^3	<25.0×10^9/L <25,000/mm^3
METABOLIC/LABORATORY				
Albumin, serum- low (hypoalbuminemia)	<LLN – 3 g/dL <LLN – 30 g/L	<3 – 2 g/dL <30 – 20 g/L	<2 g/dL <20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
ALT	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
AST	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Bilirubin (hyperbilirubinemia)	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 10.0×ULN	>10.0×ULN
Calcium, serum-low (hypocalcemia)	<LLN – 8.0 mg/dL <LLN – 2.0 mmol/L	<8.0 – 7.0 mg/dL <2.0 – 1.75 mmol/L	<7.0 – 6.0 mg/dL <1.75 – 1.5 mmol/L	<6.0 mg/dL <1.5 mmol/L
Calcium, serum-high (hypercalcemia)	>ULN – 11.5 mg/dL >ULN – 2.9 mmol/L	>11.5 – 12.5 mg/dL >2.9 – 3.1 mmol/L	>12.5 – 13.5 mg/dL >3.1 – 3.4 mmol/L	>13.5 mg/dL >3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	>ULN – 300 mg/dL >ULN – 7.75 mmol/L	>300 – 400 mg/dL >7.75 – 10.34 mmol/L	>400 – 500 mg/dL >10.34 – 12.92 mmol/L	>500 mg/dL >12.92 mmol/L
Creatinine	>ULN – 1.5×ULN	>1.5 – 3.0×ULN	>3.0 – 6.0×ULN	>6.0×ULN
GGT (γ-glutamyl transpeptidase)	>ULN – 3.0×ULN	>3.0 – 5.0×ULN	>5.0 – 20.0×ULN	>20.0×ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: >ULN – 160 mg/dL >ULN – 8.9 mmol/L	Fasting glucose value: >160 – 250 mg/dL >8.9 – 13.9 mmol/L	>250 – 500 mg/dL; >13.9 – 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	<LLN – 55 mg/dL <LLN – 3.0 mmol/L	<55 – 40 mg/dL <3.0 – 2.2 mmol/L	<40 – 30 mg/dL <2.2 – 1.7 mmol/L	<30 mg/dL <1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	<LLN – 2.5 mg/dL <LLN – 0.8 mmol/L	<2.5 – 2.0 mg/dL <0.8 – 0.6 mmol/L	<2.0 – 1.0 mg/dL <0.6 – 0.3 mmol/L	<1.0 mg/dL <0.3 mmol/L

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences
Potassium, serum-high (hyperkalemia)	>ULN – 5.5 mmol/L	>5.5 – 6.0 mmol/L	>6.0 – 7.0 mmol/L hospitalization indicated	>7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	<LLN – 3.0 mmol/L	<LLN – 3.0 mmol/L; symptomatic; intervention indicated	<3.0 – 2.5 mmol/L hospitalization indicated	<2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	>ULN – 150 mmol/L	>150 – 155 mmol/L	>155 – 160 mmol/L hospitalization indicated	>160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	<LLN – 130 mmol/L	N/A	<130 – 120 mmol/L	<120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	>300 – 500 mg/dL >3.42 – 5.7 mmol/L	>500 – 1000 mg/dL >5.7 – 11.4 mmol/L	>1000 mg/dL >11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	>ULN – 10 mg/dL ≤0.59 mmol/L without physiologic consequences	N/A	>ULN – 10 mg/dL ≤0.59 mmol/L with physiologic consequences	>10 mg/dL >0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, N/A = not applicable, LLN = lower limit of normal, ULN = upper limit of normal, WBC = white blood cell.

Based on Common Terminology Criteria for AEs (CTCAE) Version 4.0. Published: 28 May, 2009 (v4.03: 14 June, 2010).

Appendix 2 List of Permitted and Prohibited Prior/Concomitant Medications

Prohibited medications are shown in Listing 1, Listing 2, and Listing 3. Medications permitted with restrictions are listed in Listing 4, Listing 5, and Listing 6. These may not be all-inclusive listings. Please contact the medical monitor(s) if the investigators have any questions or concerns regarding any medication not listed that your subjects may be taking before enrollment or start during the course of the E2609-G000-302 study.

Antibiotics, analgesics, and anti-inflammatory drugs intended for short courses of treatment are permitted and do not need to follow the restrictions of Listing 6 for a stable dose of 4 weeks before Baseline. If these medications may affect cognitive function but the medications are clinically indicated, then cognitive testing should not take place until at least 72 hours after the last dose of the course of treatment.

Prohibited Prior/Concomitant Medications

Listing 1 Prohibited Medications Within 5 Half Lives or 7 Days, Whichever is Longer, Before Randomization Until the Last Treatment Visit

Moderate to Strong Inhibitors of Carboxylesterase 2 (CES2) Enzyme Activity
Generic name
Loperamide
Orlistat
Telmisartan
Fenofibrate
Carvedilol
Manidipine
Diltiazem
Verapamil

NOTE: Simvastatin use is permitted only with once daily evening administration.

Listing 2 Prohibited Medications Within 5 Half Lives or 60 Days, Whichever is Longer, Before Baseline Until the Last Treatment Visit

Systemic Immunosuppressants[a] and Immunoglobulin therapy	
Prednisolone	Deltasone, Prednicot, Prednisone Intensol, Rayos, Sterapred, Sterapred DS
Methylprednisolone	Medrol, Meprolone
Dexamethasone	Decadron, Dexasone, Diodex, Hexadrol, Maxidex
Azathioprine	Azasan, Imur
Mycophenolate	CellCept, Myfortic
Fingolimod	Gilenya
Methotrexate	Trexall
Ciclosporine	Gengraf, Neoral
Ranibizumab	Lucentis
Bevacizumab	Avastin
Infliximab	Remicade
Etanercept	Enbrel
Adalimumab	Humira
Omalizumab	Xolair
Efalizumab	Raptiva
Immune globulin IV, IVIG, IGIV	Carimune, Flebogamma, Gamimune N, Gammagard, Gamunex, Gammar-P IV, Iveegam, Octagam, Panglobulin, Vigam, Polygam S/D, Privigen, Sandoglobulin, Venoglobulin-S
Other monoclonal antibodies not listed here	

[a]Topical and inhaled formulations with minimal systemic exposure need not be prohibited.

Listing 3 Prohibited Live/Live Attenuated Vaccines Within 3 Months Before Randomization Until the Last Treatment Visit (this does not apply to non-live/inactivated vaccines)

Bacterial vaccines	**Viral vaccines**
Bacillus Calmette-Guérin vaccine against tuberculosis	Measles vaccination
Typhoid vaccination (oral)	Mumps vaccination
Cholera vaccination (oral)	Rubella vaccination
	Oral polio vaccination (Sabin)
	Yellow fever vaccination
	Varicella (chickenpox) vaccination
	Rotavirus vaccination
	Japanese encephalitis vaccination
	Live attenuated influenza vaccine (FluMist in the United States and Canada, and Fluenz in Europe)

This list is not exhaustive

Permitted Prior/Concomitant Medications

Listing 4 Medications Which Need To Be on a Stable Dose for 12 Weeks Before the Cognitive Assessments at Visit 2 and Should Remain on the Same Stable Dose From Visit 2 to Follow Up Visit 15

Cognitive Enhancers	
Donepezil	Aricept
Rivastigmine	Exelon
Galantamine	Reminyl
Memantine	Namenda

Listing 5 Permitted Medications Used on PRN Basis Which are not to be Used Within 72 Hours Before Cognitive Testing

Generic name	Trade name
Opiates	
Morphine	Astramorph PF, Avinza, Depo Dur, Duramorph, Infumorph, Kadian, MS Contin, MSIR, Oramorph SR, RMS, Roxanol
Opiate Agonists	
Meperidine	Demerol, Meperitab
Fentanyl	Actiq, Duragesic, Fentora, Onsolis, Sublimaze
Codeine	Codeine
Oxycodone	Dazidox, Endocodone, Eth-OxyDose, OxyContin, OxyFast, OxyIR, Percolone, Roxicodone, Roxicodone Intensol
Other opioids or opioid agonists which are used on PRN basis	
Benzodiazepines and sedatives	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	(various)
Zolpidem	Ambien; others
Ramelteon	Rozerem
Amitriptyline	(various)
Dothiepin	(various)
Risperidone	Risperdal
Olanzapine	Zyprexa
Promethazine	Phenergan; others
Other benzodiazepines, tricyclic antidepressants, antipsychotics and other drugs which are used on PRN basis as sedatives	

PRN = Pro re nata

This list is not exhaustive

Listing 6 Permitted Medications

If to be used on a PRN basis see Listing 5. If to be used chronically, subjects must be on a stable dose for equal or greater than 4 weeks before Randomization. Changes in dose or initiation of new concomitant medications for chronic use (not PRN use) is permitted but if the medication affects cognitive function, do not conduct cognitive testing until the dose is stable for 4 weeks.	
Generic Name	**Trade Name**
Antidepressants	
Bupropion	Aplenzin, Budeprion, Buproban, Zyban, Wellbutrin
Nefazodone	Serzone
Rasagiline	Azilect
Selegiline	EMSAM
Isocarboxazid	Marplan
Phenelzine	Nardil
Tranylcypromine	Parnate
Citalopram	Celexa
Fluvoxamine	Luvox
Escitalopram	Lexapro
Paroxetine	Paxil, Pexeva
Fluoxetine	Prozac, Sarafem, Selfemra
Sertraline	Sertaraline, Zoloft
Duloxetine	Cymbalta
Venlafaxine hydrochloride	Effexor
Desvenlafaxine	Pristiq
Amitriptyline hydrochloride	Elavil
Clomipramine hydrochloride	Anafranil
Desipramine hydrochloride	Norpramin
Doxepin hydrochloride	Prudoxin, Silenor, Sinequan, Zonalon
Imipramine hydrochloride	Tofranil
Nortriptyline hydrochloride	Aventyl, Pamelor
Trimipramine maleate	Surmontil
Protriptyline hydrochloride	Vivactil
Amoxapine	Amoxapine
Trazodone hydrochloride	Desyrel, Oleptro
Maprotiline hydrochloride	Ludiomil
Mirtazapine	Remeron Soltab

Listing 6 Permitted Medications

Generic Name	Trade Name
Mood Stabilizers	
Carbamazepine	Carbatrol, Epitol, Equetro, Tegretol, Tegretol XR
Lamotrigine	Lamictal, Lamictal CD, Lamictal ODT, Lamictal XR
Valproic acid	Depacon, Depakene, Depakote, Depakote ER, Divalproex Sodium, Stavzor, Valproate
Antipsychotics	
Acetophenazine	Tindal
Aripiprazole	Abilify
Asenapine	Saphris
Olanzapine	Zyprexa
Chlorpromazine	Thorazine
Haloperidol	Haloperidol, Haldol
Clozapine	Clozaril, Fazaclo
Fluphenazine	Prolixin
L-Methylfolate	Deplin, L-Methylfolate Calcium
Loxapine	Loxitane
Mesoridazine	Serentil
Perphenazine	Trilafon
Quetiapine	Seroquel
Risperidone	Risperdal
Thioridazine	Mellaril
Thiothixene	Navane
Trifluoperazine	Stelazine
Benzodiazepines	
Estazolam	ProSom
Alprazolam	Alprazolam Intensol, Niravam, Xanax
Triazolam	Halcion
Midazolam	Versed
Lorazepam	Ativan
Flunitrazepam	Rohypnol
Temazepam	Restoril
Clonazepam	Ceberclon, Klonopin
Diazepam	Diastat, Dizac, Valium
Chlordiazepoxide	H-Tran, Librium
Flurazepam	Dalmane
Zopiclone	
Zopidem	

PRN = Pro re nata

Appendix 3 AEs Indicating Signals of Possible Drug Abuse Potential

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
1	**Euphoric mood**	Euphoric mood
		Euphoria
		Euphoric
		Exaggerated well-being
		Excitement excessive
		Feeling high
		Felt high
		High
		High feeling
		Laughter
2	**Elevated mood**	Elevated mood
		Mood elevated
		Elation
3	**Feeling abnormal**	Feeling abnormal
		Cotton wool in head
		Feeling dazed
		Feeling floating
		Feeling strange
		Feeling weightless
		Felt like a zombie
		Floating feeling
		Foggy feeling in head
		Funny episode
		Fuzzy
		Fuzzy head
		Muzzy head
		Spaced out
		Unstable feeling
		Weird feeling
		Spacey
4	**Feeling drunk**	Feeling drunk
		Drunkenness feeling of
		Drunk-like effect
		Intoxicated
		Stoned
		Drugged
5	**Feeling of relaxation**	Feeling of relaxation
		Feeling relaxed
		Relaxation
		Relaxed
		Increased well-being
		Excessive happiness

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
6	**Thinking abnormal**	Thinking abnormal
		Abnormal thinking
		Thinking irrational
		Thinking disturbance
		Thought blocking
		Wandering thoughts
7	**Hallucination**	Hallucination
		Illusions
		Flashbacks
		Floating
		Rush
		Feeling addicted
8	**Inappropriate affect**	Elation inappropriate
		Exhilaration inappropriate
		Feeling happy inappropriately
		Inappropriate affect
		Inappropriate elation
		Inappropriate laughter
		Inappropriate mood elevation
9	**Mood disorders and disturbances**	Mental disturbance
		Depersonalisation
		Psychomotor stimulation
		Mood disorders
		Emotional and mood disturbances
		Delirium
		Delirious
		Mood altered
		Mood alterations
		Mood instability
		Mood swings
		Emotional lability
		Emotional disorder
		Emotional distress
		Personality disorder
		Impatience
		Abnormal behavior
		Delusional disorder
		Irritability
10	**Drug tolerance**	Drug tolerance
		Habituation
		Drug withdrawal syndrome
		Substance-related disorders
11	**Psychosis**	Psychosis
		Psychotic episode or disorder

	Category	Examples of AEs Indicating Signals of Possible Drug Abuse Potential
12	**Dissociative State**	Dissociation
		Disconnected
		Derealisation
		Depersonalisation
		Detached
		Sensation of distance from one's environment
		Loss of a sense of personal identity

Appendix 4 Pharmacodynamic, Pharmacogenomic, and Other Biomarker Research

Subjects enrolled in this clinical study will have biologic samples collected for PD, PGx, and other biomarker analysis. These samples may be used for discovery and validation to identify biomarkers that may be used for exploratory evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

The PGx samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential AEs related to study drug, and to explore the role of genetic variability in response. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug PK or therapeutic response.

Collection of the PD, PGx, and other biomarker samples will be bound by the sample principles and processes outlined in the main study protocol. Sample collection for PD, PGx, and other biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

Sample Collection and Handling

The samples will be collected according to the study flow chart. If, for operational or medical reasons, the genomic DNA blood sample cannot be obtained at the prespecified visit, the sample can be taken at any study center visit at the discretion of the investigator and site staff.

Security of the Samples, Use of the Samples, Retention of the Samples

Sample processing, for example DNA and/or RNA extraction, genotyping, sequencing, or other analysis will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored for up to 15 years after the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

It is possible that future research and technological advances may identify genomic variants of interest, or allow alternative types of genomic analysis not foreseen at this time. Because it is not possible to prospectively define every avenue of future testing, all samples collected will be single or double coded (according to the ICH E15 guidelines) in order to maintain subject privacy.

Right to Withdraw

If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All PD and other biomarker samples will be single coded. Genomic DNA samples used to explore the effects on PK, treatment response, and safety will be single coded. Genomic DNA samples that will be stored for long-term use (defined as 15 years after the completion of the study) will be double coded. Double coding involves removing the initial code (subject identifier [ID)] and replacing with another code such that the subject can be re-identified by use of 2 code keys. The code keys are usually held by different parties. The key linking the sample ID to the subject number will be maintained separately from the sample. At this point, the samples will be double-coded, the first code being the subject number. Laboratory personnel performing genetic analysis will not have access to the "key." Clinical data collected as part of the clinical trial will be cleaned of subject identifying information and linked by use of the sample ID "key."

The sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- CROs retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the PD, PGx, and other biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

If at any time, PD, PGx, and/or other biomarker results are obtained that may have clinical relevance, IRB review and approval will be sought to determine the most appropriate manner of disclosure and to determine whether or not validation in a Clinical Laboratory Improvement Amendments-certified setting will be required. Sharing of research data with individual patients should only occur when data have been validated by multiple studies and testing has been done in Clinical Laboratory Improvement Amendments-approved laboratories.

PROTOCOL SIGNATURE PAGE

Study Protocol Number: E2609-G000-302

Study Protocol Title: A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease

Investigational Product Name: E2609

IND Number: 109308

EudraCT Number: 2016-004128-42

SIGNATURES

Authors:

PPD

Date

Eisai Ltd.

PPD

Date

Eisai, Inc.

PPD

Date

Eisai Inc.

INVESTIGATOR SIGNATURE PAGE

Study Protocol Number:	E2609-G000-302
Study Protocol Title:	A Placebo-Controlled, Double-Blind, Parallel-Group, 24-Month Study to Evaluate the Efficacy and Safety of E2609 in Subjects with Early Alzheimer's Disease
Investigational Product Name:	E2609
IND Number:	109308
EudraCT Number:	2016-004128-42

I have read this protocol and agree to conduct this study in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date