16.1.9 Documentation of Statistical Methods

The final approved Statistical Analysis Plan and other statistical documents, as applicable, for these studies are provided in the following pages.

- Statistical Analysis Plan v2.0, 19 Mar 2020
- Statistical Analysis Plan v1.0 for E2609-G000-301, 17 Mar 2017
- Statistical Analysis Plan v1.0 for E2609-G000-302, 17 Mar 2017
- Data Safety Monitoring Board (DSMB) Elenbecestat (E2609) Program Charter, 17 Feb 2017
- Appendix 9 to DSMB Elenbecestat Program Charter, 11 Sep 2019
- Appendix 9 to DSMB Elenbecestat Program Charter, 27 Mar 2019
- Appendix 9 to DSMB Elenbecestat Program Charter, 07 Nov 2018
- DSMB Chair Recommendation form for E2609-G000-301 and E2609-G000-302, 11 Sep 2019
- DSMB Chair Recommendation form for E2609-G000-301, 27 Mar 2019
- DSMB Chair Recommendation form for E2609-G000-302, 27 Mar 2019
- DSMB Chair Recommendation form for E2609-G000-301, 10 Dec 2018
- DSMB Chair Recommendation form for E2609-G000-302, 10 Dec 2018
- DSMB Chair Recommendation form for E2609-G000-301 and E2609-G000-302, 07 Sep 2018
- DSMB Chair Recommendation form for E2609-G000-301, 23 May 2018
- DSMB Chair Recommendation form for E2609-G000-302, 23 May 2018
- DSMB Chair Recommendation form for E2609-G000-301, 27 Feb 2018
- DSMB Chair Recommendation form for E2609-G000-302, 27 Feb 2018
- DSMB Chair Recommendation form for E2609-G000-301, 20 Nov 2017
- DSMB Chair Recommendation form for E2609-G000-302, 20 Nov 2017
- DSMB Chair Recommendation form for E2609-G000-301, 08 Aug 2017

- DSMB Chair Recommendation form for E2609-G000-302, 08 Aug 2017
- DSMB Chair Recommendation form for E2609-G000-301, 12 Apr 2017
- DSMB Data Review Meeting Minutes (Open Session Minutes), 11 Sep 2019
- DSMB Data Review Meeting Minutes (Open Session Minutes), 27 Mar 2019
- DSMB Data Review Meeting Minutes (Open Session Minutes), 10 Dec 2018
- DSMB Data Review Meeting Minutes (Open Session Minutes), 07 Sep 2018
- DSMB Data Review Meeting Minutes (Open Session Minutes), 23 May 2018
- DSMB Data Review Meeting Minutes (Open Session Minutes), 27 Feb 2018
- DSMB Data Review Meeting Minutes (Open Session Minutes), 20 Nov 2017
- DSMB Data Review Meeting Minutes (Open Session Minutes), 08 Aug 2017
- DSMB Data Review Meeting Minutes (Open Session Minutes), 12 Apr 2017
- Data Integrity Protection Plan v3.0 for E2609-G000-301, 11 Nov 2019
- Data Integrity Protection Plan v3.0 for E2609-G000-302, 11 Nov 2019

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	E2609-G000-301/302
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
Date:	19 Mar 2020
Version:	Final Version 2.0

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
ADCOMS	Alzheimer's Disease Composite Score
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
AChEI	Acetylcholinesterase inhibitors
ANCOVA	analysis of covariance
ApoE	apolipoprotein E
BMI	body mass index
CBB	Cogstate Brief Battery
C-CASA	Columbia- classification algorithm of suicide assessment
CI	confidence interval
CDR	Clinical Dementia Rating
CDR-SB	Clinical Dementia Rating – Sum Of Boxes
CL	clearance
CRF	case report form
CSF	cerebrospinal fluid
C-SSRS	Columbia - Suicide Severity Rating Scale
DSMB	data safety monitoring board
EAD	Early Alzheimer's Disease
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D	EuroQol-5 Dimensions
FAQ	Functional Activities Questionnaire
FAS	full analysis set
fMRI	functional magnetic resonance imaging
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ISLT	International Shopping List Task
ITT	intent to treat
IxRS	Interactive voice and web response system
LLN	lower limit of normal
LLT	lower level term
LLOQ	lower limit of quantification
LME	linear mixed effects
LS	least squares
MAR	missing at random
MCI	Mild Cognitive Impairment

MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMSE	Mini Mental State Examination
MMA	methylmalonic acid
MMRM	mixed-effects models for repeated measures
MRI	magnetic resonance imaging
NFL	neurofilament light
Ng	neurogranin
NPI	Neuropsychiatric Inventory
OLE	open-label extension
PET	positron emission tomography
PD	pharmacodynamic
PK	pharmacokinetic
PPS	per protocol analysis set
PT	preferred term
QD	once daily
QTcF	corrected QT interval calculated using Fridericia's formula
QOL-AD	Quality of Life in Alzheimer's Disease
RCI	Reliable Change Index
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SOC	system organ class
SUVR	standardized uptake value ratio
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory
TSH	Thyroid stimulating hormone
TLG	tables, listings, and graphs
ULN	upper limit of normal
ULOQ	upper limit of quantification
vMRI	volumetric magnetic resonance imaging
WHO DD	World Health Organization Drug Dictionary

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study E2609-G000-301 and study E2609-G000-302. This SAP is based on the protocol amendment 07 (23May2019, v8.0) for E2609-G00-301 and the protocol amendment 06 (23May2019, v7.0) for E2609-G00-302. "Study" indicates Core Study unless specifically described. The data from the Open-Label Extension (OLE) phase of this study will be only listed unless specified.

3.1 STUDY OBJECTIVES

3.1.1 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

3.1.2 Secondary Objectives

The key secondary objectives of the Core Study are as follows:

- 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

- 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:

- 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 the 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 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 the 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

- To determine whether elenbecestat 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 pooled across studies E2609-G000-301 and E2609-G000-302

- To determine whether elenbecestat is superior to placebo on the ADAS-cog$_{14}$ 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-cog$_{14}$, 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 [ptau], 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

Based on the DSMB analyses, the evaluation of ADAS-cog$_{11}$ will be added as one of other secondary objectives of the Core Study.

The following secondary objective will be added to evaluate change from last dose in clinical assessments instead of the analysis for the change from baseline in CDR-SB at 27 months described above.

- To evaluate the change after last dose in CDR-SB, ADCOMS, ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

As the study E2609-G000-301 and study E2609-G000-302 were terminated early there is a smaller sample size than originally planned, therefore the following key secondary objective will be removed:

- 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 each study (E2609-G000-301 and E2609-G000-302)

As the study E2609-G000-301 and study E2609-G000-302 were terminated early, the following objective will not be conducted:

- To evaluate the population pharmacokinetics (PK) of elenbecestat in subjects with EAD

The analyses for the following objectives will be reported separately from the CSR because of the timing of data availability.

- To evaluate the relationship between clinical changes at 24 months (CDR-SB, ADCOMS, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in functional magnetic resonance imaging [fMRI]) at 24 months in subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

3.1.3 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

- 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

- To explore potential plasma and CSF biomarkers of AD (eg, neurofilament [NFL] and neurogranin [Ng])

- To evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months
- 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
- To explore the relationship between exposure (in CSF, plasma) of elenbecestat 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

If the data available for the analysis is not sufficient, the analyses for the following objectives may not be performed or modified to focus on other visit than 24 months.

- To determine whether elenbecestat is superior to placebo on brain tau pathology at 24 months as measured by tau PET in subjects with EAD
- 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 evaluate the correlation between the effect of elenbecestat on brain tau pathology with the effect on CSF biomarkers of neurodegeneration at 24 months
- 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 if a trend with time of treatment is noted with the biomarker than the following objective will be conducted graphically.

- To explore the relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease (AD), as deemed appropriate

The analyses for the following objectives will be reported separately from the CSR because of the timing of data availability.

- 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

3.1.4 Exploratory Objectives

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) in the subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302, as deemed appropriate

- To evaluate whether elenbecestat is superior to placebo in reducing the initiation or dose increase of other AD pharmacotherapies in the subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

- To evaluate whether elenbecestat is superior to placebo over time and at 24 months on change on the Neuropsychiatric Inventory (NPI) 10 item in the subjects with EAD pooled across studies E2609-G000-301 and E2609-G000-302

- 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

As the study E2609-G000-301 and study E2609-G000-302 were terminated early there is a smaller sample size than originally planned, therefore the statistical comparisons to evaluate QoL assessments (EQ-5D, QOL-AD, Zarit's Burden Interview) will not be performed.

As the study E2609-G000-301 and study E2609-G000-302 were terminated early, the following objective will not be conducted

- To explore the relationship between elenbecestat exposure/pharmacodynamics (PD) (in CSF, plasma) with efficacy and safety endpoints (eg, immune function) in the subjects

with EAD pooled across studies E2609-G000-301 and E2609-G000-302, as deemed appropriate

3.2 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 mild cognitive impairment (MCI) due to 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.

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 (in 1:1 randomization ratio) for 24 months. Randomization will be stratified according to region (7 levels), clinical disease 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 Oceania region and South Africa)
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.

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 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.

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

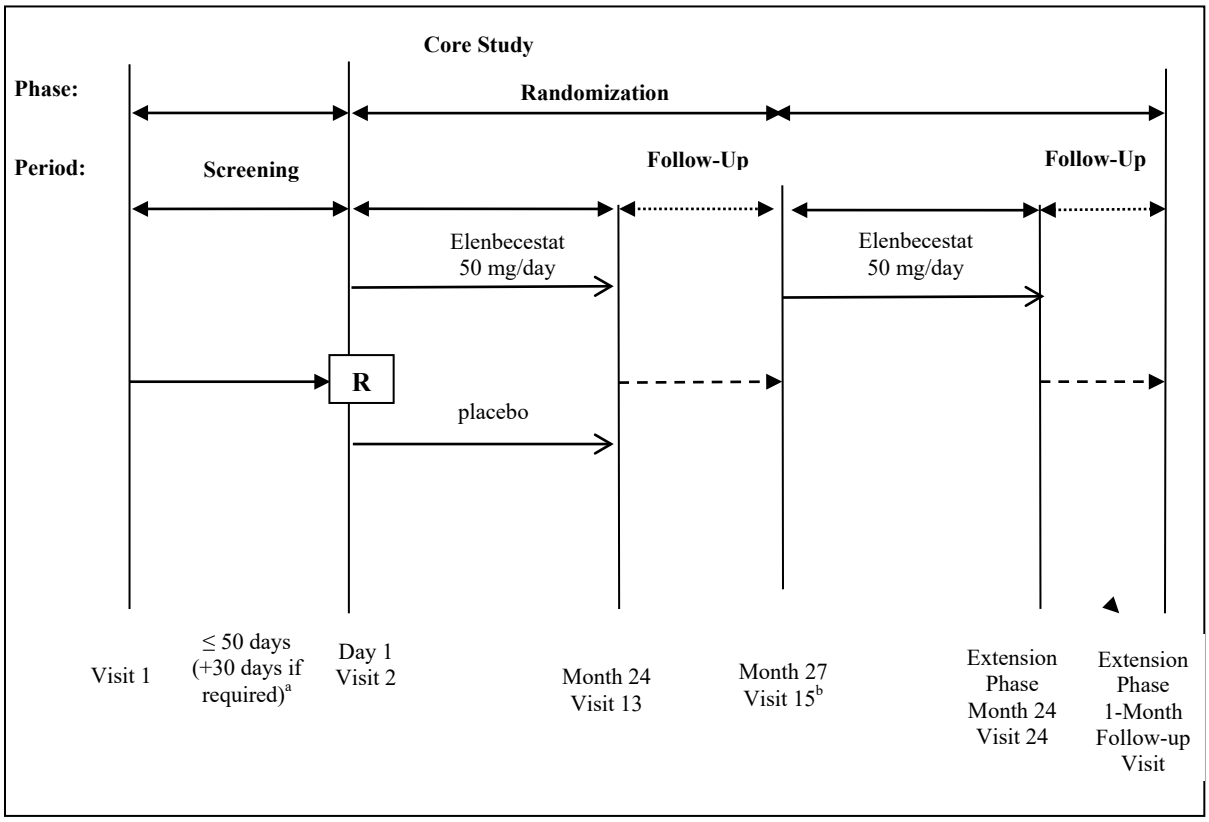
The Randomization Phase consists of a Treatment Period and a Follow-Up Period. The Treatment Period will last 24 months. Subjects will be randomized at Visit 2 (Day 1) to receive elenbecestat 50 mg per day or placebo administered orally, once daily (QD) in the morning with or without food. The Follow-up 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.

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 discontinued study drug between 12 and 24 months of treatment will be asked to return to the clinic for a 24 month clinical assessment.

Eligible subjects may enter the Extension Phase immediately following the completion of Visit 15 (final follow-up visit) 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.

Figure 1 Study Design of E2609-G000-301/302



Elenbecestat = Test drug, 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

4 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 Alzheimer's Disease Neuroimaging Initiative (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 the elenbecestat compared to placebo with a 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.

5 STATISTICAL METHODS

Statistical analyses will be performed by the sponsor or designee after the Core 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 for study disposition, demographic and baseline characteristics, primary endpoint, secondary endpoints, extent of exposure and key adverse event tables. The details are specified in Table, Listing and Graph (TLG) shell. Statistical analyses will be performed using Statistical Analysis System (SAS) software or other validated statistical software as required. All statistical tests will be based on the 5% (2-sided) level of significance.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 STUDY ENDPOINTS

5.1.1 PRIMARY ENDPOINT

- Change from baseline in the CDR-SB at 24 months in the combined studies

5.1.2 SECONDARY ENDPOINTS

The key secondary endpoints of the study are as follows

- 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

- 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-cog$_{14}$, MMSE, and FAQ at 24 months in the combined studies

- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in the combined studies

Based on the DSMB analyses, the change from baseline in ADAS-cog$_{11}$ will be added as one of other secondary endpoints.

The following secondary endpoint will be added to evaluate the change after last dose instead of the change from baseline in CDR-SB at 27 months described above.

- Change from last dose to follow-up in CDR-SB, ADCOMS, ADAS-cog$_{11,}$ ADAS-cog$_{14}$, MMSE, ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) in the combined studies

As the study E2609-G000-301 and study E2609-G000-302 were terminated early, the sample size for amyloid PET SUVR is smaller than originally planned. Therefore the following key secondary endpoint will be removed.

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

5.1.3 BIOMARKER ENDPOINTS

- Change from baseline in tau PET signal at 24 months

- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months

- Change from baseline in CSF amyloid biomarkers Aβ(1-x), Aβ(1-42), and Aβ(1-40) at 24 months

- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x)) at all assessments

- Change from baseline in plasma NFL and CSF NFL and Ng
- Change from baseline in vMRI parameters (eg, total hippocampal volume etc.) at 24 months using vMRI
- Change from baseline in the preservation of connectivity on fMRI at 24 months

If the available data for the analysis is not sufficient, the analyses for the following endpoints may not be performed or may be performed at only other visits than 24 months.

- Change from baseline in tau PET signal at 24 months
- Change from baseline in CSF biomarkers t-tau and p-tau at 24 months
- Change from baseline in CSF amyloid biomarkers Aβ(1-x), Aβ(1-42), and Aβ(1-40) at 24 months
- Change from baseline in CSF biomarkers (eg, NFL, and Ng)

The analyses for the following endpoint will be reported separately from the CSR because of the timing of data availability.

- Change from baseline in the preservation of connectivity on fMRI at 24 months

5.1.4 EXPLORATORY ENDPOINTS

- Time to change of concomitant AD treatment (ie, dose increase and/or initiation of treatment with Acetylcholinesterase inhibitors [AchEI] or memantine after randomization) by 24 months in the combined studies
- The proportion of subjects at 24 months who received dose increases and/or initiation of treatment with AChEI or memantine after randomization in the combined studies
- The rate of change over time (mean slope) based on NPI-10 item score over 24 months in the combined studies
- Change from baseline in NPI-10 item at 24 months in the combined studies
- 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 in the combined studies
- Change from baseline in Zarit's Burden Interview at 24 months in the combined studies

5.2 STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

The definitions of the analysis data sets are:

- 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. Safety Analysis Set will be used in the statistical analyses for safety. In the event that a subject received study drug different from the one to which this subject was randomized, the subject's safety data will be analyzed "as treated."
- 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. PPS will be used to conduct a sensitivity analysis of the primary efficacy endpoint. The criteria for exclusion from PPS are listed below:
    - MMSE <24 or CDR global score ≠ 0.5 or CDR Memory Box score < 0.5 at screening
    - Condition that may contribute to cognitive impairment at screening
        - vascular dementia, lewy body dementia, PD, multiple sclerosis, epilepsy in medical history
        - Hachinski Score >4
    - Brain MRI exclusions
        - BMW Section 4 Other MRI Abnormalities exclusions including:
            - Superficial siderosis
            - Lacunar infarct (2 or more)
            - Stroke involving a major vascular territory

              (Defined by safety MRI data)
    - ISLT total recall and delayed recall impairment < 1 SD from age-adjusted norms at screening
    - Negative for amyloid pathology for all assessments performed at screening, ie PET and/or CSF.
    - Subject <50 or >85 years of age at consent
    - Subject was receiving AChEIs or memantine or both for AD but had not been on a stable dose for at least 12 weeks prior to baseline
    - At screening
        - Thyroid stimulating hormone (TSH) > upper limit of normal (ULN)

        - Vitamin B12 < lower limit of normal (LLN) and methylmalonic acid MMA >0.41μm/L (if MMA available)
    - Illiteracy in medical history
    - Study drug compliance
        - < 67% up to planned last dose
- 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. The separate analysis set will be prepared for amyloid PET, tau PET, plasma, CSF, and vMRI assessments.

The number (percent) of subjects included in each analysis set will be presented by treatment group and combined total for each analysis set.

The subjects who enroll into the OLE phase and receive at least 1 dose of OLE study drug will be considered as "All Safety Subjects" for OLE, which will be used for OLE tables mainly.

5.2.2 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 electronic case report form (eCRF). The primary reasons for screen failures (did not meet inclusion or met exclusion criteria, adverse event (AE), lost to follow-up, withdrawal of consent, and other) will be presented. The distribution of the number of randomized subjects enrolled by each site, country, and region will be summarized for each randomized treatment group and combined total.

Study Completion: the number (percent) of randomized and treated subjects who completed the study and who withdrew from the study will be summarized according to the primary reason for withdrawal and secondary reason(s) for withdrawal, based on data reported on the Subject Disposition (Study Phase) case report form (CRF). The number (percent) will be presented by treatment group and total subjects; randomized, not treated, treated, who completed the study, and withdrew from the study. The primary reasons for early withdrawal from the study are: AE, lost to follow-up, subject choice, inadequate therapeutic effect, withdrawal of consent, pregnancy, study terminated by sponsor, and other. The secondary reasons for early withdrawal from the study are: AE, subject choice, inadequate therapeutic effect, and other. This table will be summarized on the All Randomized Subjects, the Safety Analysis Set, and the FAS.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study drug and who discontinued early from study drug will be summarized according to the primary reason for early discontinuation (ED) 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 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, inadequate therapeutic effect, pregnancy, and other. The secondary reasons for early discontinuation from the study drug are: AE, subject choice, inadequate therapeutic effect, and other. This table will be summarized on the All Randomized Subjects, the Safety Analysis Set, and the FAS.

The subject disposition for the OLE phase will be summarized in the same way.

5.2.3 Protocol Deviations

A listing of subjects with major protocol deviations will be provided by subject along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock. Major protocol deviations will be summarized by treatment group and combined total.

5.2.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the Safety Analysis set and FAS will be summarized by treatment group using descriptive statistics.

Continuous demographic and baseline variables include: age (years), baseline height (cm) and weight (kg), body mass index (BMI) (kg/m^2), CDR-SB score, ADAS-cog_{11}, ADAS-cog_{14}, ADAS-cog_{14} Word List, ADCOMS, MMSE, ISLT z-score (total recall, delayed recall), Cogstate Brief Battery (CBB) z-score (accuracy of one-card learning, speed of one-back memory, speed of detection, speed of identification), FAQ, years since onset of cognitive impairment symptoms, and years since disease diagnosis, education in years.

Categorical variables include: age group (<65, ≥65 to <80, and ≥80), sex, race, ethnicity, region, concurrent AD medication use (yes, no), clinical disease staging (MCI due to AD, early stages of mild AD), apolipoprotein E (*ApoE)* 4 status, CDR Memory Box score and CDR-SB score (0 to 1.5, 2 to 3.5, 4 to 5.5, 6 or more).

Date of disease diagnosis will be defined as the date of current diagnosis on the Cognitive Impairment History and Current Diagnosis eCRF or the date of diagnosis of mild cognitive impairment on the Medical History and Current Medication Condition eCRF, whichever is earlier.

Region, concurrent AD medication use, and clinical disease staging will be summarized using the actual classification, not the interactive voice and web response system (IxRS) classification.

Baseline in PD/biomarkers for All Randomized Subjects will be summarized by treatment group and combined total using descriptive statistics.

For OLE, demographic and baseline characteristics for All Safety Subjects will be summarized using descriptive statistics.

MEDICAL HISTORY

The medical history verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database. The number (percent) of subjects will be presented by preferred term and treatment group.

5.2.5 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). The number (percentage) of subjects who took prior, concomitant, current and treatment-emergent 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. Current medication will be defined as medications that started before the first dose of study drug and were continuing at the time of the first dose of study drug. Treatment-emergent concomitant medication will be defined as medications that 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 during the 12-week Follow-Up Period will also be recorded.

Prior and concomitant therapies for AD will be summarized separately.

Subjects' status on AD medications will be summarized by overall and each clinical disease staging.

5.2.6 Treatment Compliance

Treatment compliance (%) will be calculated for Safety Analysis set as follows:

$$\frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned}}{\text{Planned Total number of tablets to be taken}} * 100\%$$

Compliance will be calculated in two ways: compliance up to the planned date of last dose of study drug (compliance rate during treatment), and overall compliance rate. For compliance rate during treatment, the planned total number of tablets to be taken up to the planned date of last dose of study drug will be used as denominator. Overall compliance rate will be calculated as the 24-month compliance by assuming each subject has been followed through 24 months (729 days) in the study; a subject will be considered to take no study drug after study drug discontinuation until the end of 24 months. For overall compliance rate, 729 will be used as denominator. '999' in total number of tablets dispensed at visit is considered as 0 in the above

calculation. '999' in total number of tablets returned at visit is considered that all tablets dispensed would be returned at visit. If planned total number of tablets to be taken at visit is missing, it will be imputed by total number of tablets dispensed at visit unless total number of tablets dispensed and total number of tablets returned at visit is same.

Treatment compliance will be summarized using descriptive statistics by treatment group. Subjects will also be categorized by compliance criteria <67%, 67% to 100%, >100% to 120%, and >120%.

5.2.7 Stratification factor status

IxRS versus CRF Stratification Factors (concurrent AD medication use, clinical disease staging, region) will be summarized by treatment.

5.3 DATA ANALYSIS GENERAL CONSIDERATIONS

5.3.1 Pooling of Centers

This study has used region as a stratification factor for randomization, therefore, there is no plan to pool any other type of centers or sites.

The regions and corresponding countries that might be included and are grouped together in a particular region are:

1. North America: US, and Canada

2. Western Europe (including Oceania region and South Africa): Australia, Austria, Denmark, Finland, France, Germany, Italy, Portugal, South Africa, Spain, and United Kingdom

3. Eastern Europe: Bulgaria, Croatia, Czech Republic, Greece, Hungary, Poland, Russian Federation , and Slovakia

4. Japan

5. China

6. Other Asian countries/regions: Singapore, South Korea, and Taiwan

7. South America: Argentina, Chile, and Mexico

Czech Republic is incorrectly listed in IxRS as part of Western Europe and Australia is incorrectly listed in IxRS as part of Other Asian countries (both for E2609-G000-301). The correct list shown above will be used for the any analyses except the adjustments for covariates of interest to follow intent to treat (ITT) principle.

5.3.2 Adjustments for Covariates of Interest

The primary, secondary, and exploratory efficacy endpoints will include the stratification variables (region, concurrent AD medication use, clinical disease staging), *ApoE4* status, and baseline value of the endpoint (if applicable) as covariates. For mixed-effects models for repeated measures (MMRM), the baseline-by-visit interaction will also be included. To follow ITT principle, the classification used at randomization will be used for the adjustments for covariates of interest.

5.3.3 Multiple Comparisons/Multiplicity

The primary and key secondary endpoints 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 hierarchical order for these endpoints is:

1. Change from baseline in the CDR-SB at 24 months in the combined studies (primary endpoint)
2. Change from baseline in ADCOMS at 24 months in the combined studies
3. Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies
4. Change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the individual studies

The 4th endpoint will be excluded because of smaller sample size than original plan.

Analyses on other secondary, biomarker and exploratory endpoints will be conducted without adjustment for multiplicity.

5.3.4 Examination of Subgroups

Subgroup analysis will be performed for the primary, secondary efficacy endpoints, and biomarker endpoints. The subgroups include:

- age (<65, 65 to <80, and ≥80 years)
- sex
- race
- ethnicity
- region (section 5.3.1)
- concurrent AD medication use (yes, no) at baseline

- clinical disease staging (MCI due to AD, early stages of mild AD) at baseline
- *ApoE4* status
- baseline CDR Memory Box score
- very mild subjects (baseline CDR-SB≤1.5 and baseline MMSE≥27)
- baseline amyloid PET SUVR 1.2 to 1.6
- amyloid PET tracer (Florbetapir, Florbetaben, and Flutemetamol; only for amyloid PET SUVR)

For concurrent AD medication use, clinical disease staging, and region, the actual classification (not the IxRS classification) will be used.

As described in Section 5 Statistical methods, the efficacy will also be evaluated within each study (E2609-G000-301 and E2609-G000-302).

Forest plot for primary and key secondary endpoint (only ADCOMS) will be generated to visually display the treatment difference with 95% confidence interval, no significance tests will be performed in the subgroups.

5.3.5 Handling of Missing Data

Efficacy endpoints

The primary endpoint will be analyzed using MMRM assuming missing at random (MAR). The same method will be used for key secondary endpoints, other secondary endpoints, exploratory endpoints and biomarker endpoints if appropriate.

In addition, all missing values will be imputed using multiple imputation assuming MAR with analysis of covariance (ANCOVA) as sensitivity analysis for primary analysis. The detailed programs are shown in Section 9.

Clinical Assessment

If any item is missing within the CDR, ADCOMS, ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, FAQ, and ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) then their respective total scores will be missing.

Laboratory values

If the values include non-numerical symbols “>”, “<”, “<=” and “>=”, they will be imputed using the following rule.

- For < values impute with value - 1
- For > values impute with value + 1
- For >= values or <= values impute with value

If the least significant digit of the value is after the decimal point, increase/decrease by the smallest unit of that digit (ex. for, ">7.3", use 7.4 which is calculated by 7.3 + 0.1).

Plasma/CSF PD/Biomarkers

Values >upper limit of quantification (ULOQ) or < lower limit of quantification (LLOQ) will be imputed using ULOQ or LLOQ respectively.

5.3.6 Other Considerations

Not Applicable.

5.4 EFFICACY ANALYSES

5.4.1 Primary Efficacy Analysis

Regarding the primary endpoint, 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 based on the ITT philosophy without regard to adherence to treatment. All observed data will be included in the primary analysis, regardless of treatment discontinuation or change in concomitant AD medications. 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 MMRM on the FAS. The MMRM model will include baseline CDR-SB and baseline CDR-SB by visit interaction as a covariate, with treatment group, visit, randomization stratification variables (ie, region [7 levels], clinical disease staging [MCI due to AD, early stage of mild AD], and concurrent AD medication use at randomization (Visit 2) [yes, no]), *ApoE4* status, and treatment group-by-visit interaction as fixed effects. An unstructured covariance matrix will be employed to model the covariance of within subject effect and the Kenward-Roger approximation will be used to estimate the denominator degrees of freedom; 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. If a structured covariance is used, then the sandwich estimator will be used to estimate variance of the treatment effect estimator.

This primary analysis will include all observed post baseline data of the change from baseline in CDR-SB without imputation of missing values. The least squares (LS) means and difference in

LS means between elenbecestat treatment group and placebo, and corresponding 95% confidence interval (CI) will be presented.

Sensitivity/Supplementary Analyses

1). An MMRM analysis will be performed on the PPS.

2). To minimize the impact of intercurrent events (i.e., treatment discontinuation or change in concomitant AD medications), an MMRM analysis will be conducted on both FAS and PPS, by censoring the data after intercurrent events (i.e., treatment discontinuation, initiation of new AD medications [AChEI or memantine] and/or change in dose of current AD medications).

3). An ANCOVA model will be used after multiple imputation (MI) to evaluate the impact of missing data in both FAS and PPS. The following steps are described for multiple imputation.

Step 1 (imputing missing data): The dataset will be converted into monotone missing pattern by imputing intermediate missing data using MCMC approach first. The monotone data will then be imputed with monotone regression method. The imputation regression model will include treatment group, baseline CDR-SB and all available change from baseline in CDR-SB at post-baseline visits. There will be 1000 imputations, ie, 1000 imputed completed datasets, created with a predefined seed number (seed=2609). SAS PROC MI will be used to implement the imputation procedure. The sample SAS statement can be found in Section 9.

Step 2 (performing ANCOVA using each imputed dataset): The ANCOVA model with factors of treatment group, randomization stratification variables (ie, region [7 levels], clinical disease staging [MCI due to AD, early stage of mild AD], and concurrent AD medication use at randomization (Visit 2) [yes, no]), *ApoE4* status, and baseline CDR-SB as a covariate will be applied to each imputed dataset. SAS PROC MIXED will be used for the ANCOVA. The sample SAS statement can be found in Section 9.

Step 3 (combine results): Resulting treatment effect parameter estimators and standard errors from each of 1000 multiple imputed datasets from Step 2 will be combined using SAS PROC MIANALYZE to obtain the pooled treatment effect and variance parameter estimators according to Rubin's rules (Rubin, 1987). The sample SAS statement can be found in Section 9.

5.4.2 Secondary Efficacy Analyses

Key Secondary Endpoint Analysis

If the primary endpoint is statistically significant, then key secondary endpoints will be tested in the following order: change from baseline in ADCOMS at 24 month in the combined studies, and change from baseline in amyloid PET SUVR at 24 months for brain amyloid levels in the combined studies. Each test will be performed at a significance level of alpha 0.05 (2-sided) and will only be performed if the preceding test is statistically significant. The MMRM described for primary efficacy analysis will be used on the FAS to test the key secondary endpoints, using baseline value corresponding to the response variable in the model. For ADCOMS, The MMRM

analysis will be conducted on FAS, by censoring the data after intercurrent events as sensitivity analyses.

The amyloid PET SUVR from three tracers (Florbetapir, Florbetaben, and Flutemetamol) will be standardized using the centiloid scale and combined for the key secondary endpoint. The following equations are used to get centiloid scale in mean composite SUVR for each tracer (Adamczuk, 2019).

- Florbetapir: mean composite SUVR in centiloid scale = 205.72 * mean composite SUVR - 209.63
    - Mean composite SUVR is simple average of cingulate, frontal, parietal, and temporal rollups
    - Whole cerebellum region is used as reference region
- Florbetaben: mean composite SUVR in centiloid scale = 175.57 * mean composite SUVR - 173.21
    - Mean composite SUVR is simple average of cingulate, frontal, parietal, and temporal rollups
    - Whole cerebellum region is used as reference region
- Flutemetamol: mean composite SUVR in centiloid scale = 145.58 * mean composite SUVR - 139.29
    - Mean composite SUVR is simple average of cingulate, frontal, parietal, and temporal rollups
    - Whole cerebellum region is used as reference region

Other amyloid PET SUVR parameters (i.e.., mean composite SUVR described above using whole cerebellum, cerebellar grey matter, or subcortical white matter as separate reference region for Florbetapir and Flutemetamol and mean composite SUVR, which is simple average of cingulate, frontal, parietal, temporal, and occipital rollups, using whole cerebellum, cerebellar grey matter, or subcortical white matter as separate reference region for Florbetaben) will be summarized by tracer as biomarker endpoints using the same statistical method.

Other Secondary Endpoint Analysis

Time to worsening of CDR scores by 24 months

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using a Cox regression model for treatment effect, adjusting for randomization stratification factors. Median, 1st quartile, and 3rd quartile of time to worsening of CDR scores and proportion of subjects with

worsening of CDR scores at 6, 12, 18, and 24 months will be estimated using Kaplan-Meier method based on time to worsening of CDR scores. Time to worsening of CDR scores is defined as time from randomization to worsening of the CDR scores (ie, the second worsening - increase from baseline by at least 0.5 points on the global CDR score, in 2 consecutive visits [at least 8 weeks apart]. For example, if the global CDR scores are 0.5 at baseline, 1.0 at Visit 6 [3 months visit], 1.0 at Visit 7 [6 months visit], this subject have worsening of CDR scores at Visit 7 [6 months visit]. If the global CDR scores are 0.5 at baseline, 1.0 at Visit 6 [3 months visit], 0.5 at Visit 7 [6 months visit], the subject does NOT have worsening of CDR scores at Visit 7 [6 months visit]). If randomization date is not same as the first dose date, the first dose date will be used instead of randomization date. If last available assessment shows worsening of the global CDR score, it will be considered as a censor. For subjects whose CDR scores have not worsened by the end of study, the time to worsening of CDR scores will be censored at the date of last CDR assessment for these subjects. All post-baseline assessments within Study Day 753 (upper limit of 24 months analysis visit for CDR assessment) will be included.

The same analysis by censoring the data after intercurrent events (treatment discontinuation, and initiation/change of AD medications) will be conducted as sensitivity analysis.

Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

This endpoint will be analyzed on the FAS using a Cox regression model for treatment effect, adjusting for randomization stratification factors. Median, 1st quartile, 3rd quartile of time to conversion to dementia and proportion of subjects with dementia diagnosis at 6, 12, 18, and 24 months will be estimated using Kaplan-Meier method based on time to conversion to dementia in clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at baseline is defined as time from randomization to conversion to dementia in clinical diagnosis. If randomization date is not same as the first dose date, the first dose date will be used instead of randomization date. For subjects without clinical dementia by the end of study, the time to conversion to dementia will be censored at the date of last dementia diagnosis for these subjects. All post-baseline assessments within Study Day 753 (upper limit of 24 months analysis visit for CDR assessment) will be included.

The same analysis by censoring the data after intercurrent events (treatment discontinuation, and initiation/change of AD medications) will be conducted as sensitivity analysis.

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 rate of change over time (mean slope) based on CDR-SB score over 24 months

The rate of change over time (mean slope) for the change from baseline in CDR-SB will be analyzed on the FAS 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 assessment time, and treatment group-by-assessment time as well as random intercept and slope (unstructured). The Kenward-Roger approximation will be used to estimate the denominator degrees of freedom.

Other continuous endpoints

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

- 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
- Change from baseline in ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, and FAQ at 24 months in the combined studies
- Change from baseline in ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) at 24 months in the combined studies

The following amyloid PET mean composite SUVR in centiloid scale (Adamczuk, 2019) will be used to enrich the population, extrapolated from the 1.2 to 1.6 SUVR calculated for Florbetapir (Dhadda, 2018) : 37.234 to 119.522 (equivalent to 1.198633 to 1.667324 in Florbetaben and 1.212557 to 1.777799 in Flutemetamol) (Adamczuk [2019])

With regard to the change from baseline in ADAS-cog$_{14}$ Word List, it includes the immediate and delayed recall tasks, their scores will be part of the ADAS-cog$_{14}$ assessment (Item 1 and 4).

For ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, FAQ, and ADAS-cog$_{14}$ Word List (immediate recall and delayed recall), the MMRM analysis will be conducted on FAS, by censoring the data after intercurrent events (treatment discontinuation, and initiation/change of AD medications) as sensitivity analyses.

The MMRM using the change from baseline at last on treatment visit and 12 week Follow-up visit will be conducted based on the subjects in FAS who have the assessments at both visits to evaluate the change after last dose in CDR-SB, ADCOMS, ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, and ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) instead of the analysis for the change from baseline in CDR-SB at 27 months. The same MMRM as the primary efficacy analysis (except excluding baseline by visit interaction) will be used with appropriate contrast to evaluate the difference between last on treatment visit and 12 week Follow-up visit by each treatment group.

5.4.3 Biomarker Analyses

The biomarker endpoints are:

- Change from baseline in tau PET signal
- Change from baseline in CSF biomarkers t-tau and p-tau
- Change from baseline in CSF amyloid biomarkers Aβ(1-x), Aβ(1-42), and Aβ(1-40)
- Change from baseline in plasma amyloid biomarker (eg, Aβ(1-x))
- Change from baseline in plasma NFL and CSF NFL and Ng
- Change from baseline in volumetric MRI parameters (eg, total hippocampal volume etc.) at 24 months

Tau PET SUVR parameters (i.e., entorhinal cortex, parietal cortex, inferior temporal cortex, amygdala, hippocampus and parahippocampal cortex using inferior cerebellum cortex as reference region; left, right and bilateral) will be summarized as biomarker endpoints. vMRI parameters (i.e., total hippocampal volume, left hippocampal volume, right hippocampal volume, whole brain volume, total ventricular volume, cortical thickness – Mayo Index) will be summarized as biomarker endpoints.

The analysis of the above endpoints will be performed by using MMRM or ANCOVA model, without adjustment for multiplicity. 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. As tau PET and CSF biomarkers will be collected once within subject at different analysis visit, the ANCOVA model with factors of treatment group, visit, treatment group-by-visit interaction, randomization stratification variables (ie, region [7 levels], clinical disease staging [MCI due to AD, early stage of mild AD], and concurrent AD medication use at randomization (Visit 2) [yes, no]), *ApoE4* status, and baseline value as a covariate will be applied.

The relationship between clinical changes (CDR-SB, ADCOMS, ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in the biomarkers (amyloid PET, tau PET, plasma PD/biomarker, CSF biomarkers, vMRI) will be evaluated using correlation analysis. In the presence of strong or moderate correlation, a linear model will be fitted to further characterize the relationship between the changes in clinical endpoints and changes in biomarkers. For tau PET and CSF biomarkers, the clinical assessments close to assessment date in tau PET or CSF biomarkers will be used.The relationship between amyloid PET and tau PET and the relationship between CSF biomarkers and tau PET will be evaluated using the same analyses described above.

Only summary statistics will be provided for CSF Aβ(1-x), CSF Aβ(1-42), and CSF Aβ(1-40) because of the limitation of available data for the analysis. If the available data for the analysis for the other CSF biomarkers and tau PET is not sufficient, the analyses for CSF biomarkers and tau PET endpoints may not be performed.

The relationship between exposure (in CSF, plasma) of elenbecestat with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated graphically only if a trend in biomarkers with time of treatment is noted..

5.4.4 Exploratory Analyses

The exploratory endpoints 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

Time to change of concomitant AD treatment will be analyzed similarly as that used for the time to conversion to dementia based on clinical diagnosis, as described in the 2nd endpoints. 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. If randomization date is not same as the first dose date, the first dose date will be used instead of randomization date. 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 24 month visit (for completers) or the date of study discontinuation (for dropouts). For subjects with dose decrease or dose stop of treatment before dose increase and/or initiation of treatment, the time to change of concomitant AD treatment will be censored at the dose decrease or dose stop date.

The proportion of subjects with any change of concomitant AD treatment at 24 months will be analyzed similarly as that used for the proportion of subjects with dementia diagnosis at 24 months, as described in section 5.4.2.

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 as that used for the rate of change over time (mean slope) for the change from baseline in CDR-SB, as described in section 5.4.2.

Analysis of the change from baseline exploratory endpoints will be performed to compare elenbecestat versus placebo by using MMRM or ANCOVA model. For each of them, the treatment effect of elenbecestat 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. These endpoints include:

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

The following endpoints will be summarized by treatment group.

- 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

5.5 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 electrodiagram (ECG) findings, out-of-range vital signs, safety MRI findings, suicidality, results of the sleep questionnaire, ADAS-cog Reliable Change Index (RCI) Alert triggered, dermatology findings, and neurological examination along with change from baseline in laboratory safety test variables, ECGs, and vital sign measurements will be summarized by treatment group.

5.5.1 Extent of Exposure

The duration of exposure to study drug will be summarized as cumulative extent of exposure in categories with 3-month increment on the Safety Analysis Set and FAS. If drug interruption occurs, then the drug interruption duration will be subtracted to calculate duration of exposure. 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.

The duration of exposure to study drug in OLE phase will be summarized on All Safety Subjects similarly.

5.5.2 Adverse Events

The AE verbatim descriptions (investigator terms from the eCRF) will be classified into standardized medical terminology using the MedDRA. AEs will be coded to the MedDRA (Version 22.0 or higher) lower level term closest to the verbatim term. The linked MedDRA PT and primary SOC are also captured in the database.

A treatment-emergent adverse event (TEAE) is defined as:

- An AE that emerges during treatment or within 4 weeks (28 days) following the last dose of study drug, having been absent at pretreatment (Baseline) or

- Reemerges during treatment or within 4 weeks (28 days) following the last dose of study drug, having been present at pretreatment (Baseline) but stopped before treatment, or

- Worsens in severity during treatment or within 4 weeks (28 days) following the last dose of study drug 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, concurrent AD medication use (yes, no), and clinical disease staging (MCI due to AD, early stage of mild 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 serious adverse events (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 treatment-emergent non-serious AEs will be summarized by MedDRA SOC and PT for each treatment group. 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. The number (percentage) of subjects with TEAEs leading to interruption of study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to interruption of study drug will be provided. The number (percentage) of subjects with TEAEs leading to concomitant treatment administration will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to concomitant treatment administration will be provided.

The number (percentage) of subjects with TEAEs of special interest will be summarized by MedDRA SOC and PT for each treatment group. TEAEs relating to abnormal dreams, nightmares, or sleep terror will be defined as TEAEs classified by the category recorded in Adverse event CRF or completing sleep/abnormal dream questionnaire. The number

(percentage) of subjects with TEAEs relating to abnormal dreams, nightmares, or sleep terror will be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with treatment-emergent SAEs relating to abnormal dreams, nightmares, or sleep terror of clinical interest will be summarized. The number (percentage) of subjects with TEAEs relating to abnormal dreams, nightmares, or sleep terror of clinical interest leading to discontinuation from study drug will be summarized. The number (percentage) of subjects with treatment-related TEAEs relating to abnormal dreams, nightmares, or sleep terror will be summarized. The frequency, time to first event, and maximum AE duration of TEAEs relating to abnormal dreams, nightmares, or sleep terror will be summarized. Time to first event will be defined as time from first dose to earliest relevant AE. Maximum AE duration will be maximum time from AE start date to AE end date in each subject.

The number (percentage) of subjects with TEAEs of cognitive special interest will be summarized by MedDRA SOC and PT for each treatment group using the following PT (Table 1).

Table 1. PT for TEAE of cognitive special interest

Amnesia	Delirium	Global Amnesia	Senile Dementia
Amnesia NEC	Dementia	Illogical Thinking	Senile Dementia NOS
Anterograde Amnesia	Dementia Alzheimer's type	Memory impairment	Short-term memory Loss
Behavioral and psychiatric symptoms of Dementia	Dementia NOS	Mental impairment	Thinking abnormal
Cognitive deterioration	Dementia NOS Aggravated	Mental Impairment NOS	Thinking abnormal NEC
Cognitive disorder	Dementia of the Alzheimer's type NOS	Mental State Abnormal Aggravated	Thinking Slowed
Cognitive disorder NEC	Dementia with Lewy Bodies	Mental Status Changes	Transient Global Amnesia
Confusion	Disorientation	Mini-Mental Status Examination Abnormal	Vascular Dementia
Confusion aggravated	Disturbance in attention	Presenile Dementia	Vascular Dementia NEC
Confusional State	Frontotemporal Dementia	Retrograde Amnesia	

TEAEs of clinical interest will be defined as below.

- Lymphocyte Related Events: all preferred terms of lymphopenia, lymphocyte count abnormal and lymphocyte count decreased.

- Skin Related Events: all preferred terms under the High Level Group Term of epidermal and dermal conditions, High Level Term of urticarias and High Level Term of panniculitides.

- SAEs in Infections and Infestations SOC: only SAE and all preferred term under the SOC of infections and infestations.

- Weight Decrease Related Events: all preferred terms of weight decreased and abnormal loss of weight.

The number (percentage) of subjects with TEAEs of clinical interest will be summarized for each treatment group. The number of (percentage) of subjects with TEAEs of clinical interest will be summarized by time of occurrence (< 3 month, 3 to < 6 month, 6 to < 9 month, 9 to < 12 month, 12 to < 15 month, 15 to < 18 month, 18 month to more). The number (percentage) of subjects with TEAEs of clinical interest will be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with treatment-emergent SAEs of clinical interest will be summarized. The number (percentage) of subjects with TEAEs of clinical interest leading to discontinuation from study drug will be summarized. The number (percentage) of subjects with treatment-related TEAEs of clinical interest will be summarized.The number (percentage) of subjects with TEAEs in OLE phase will be summarized by MedDRA SOC and PT on All Safety Subjects.

5.5.3 Laboratory Values

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters, the actual value and the change from baseline to each postbaseline visit and to the end of treatment visit and 12 week Follow-up visit will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to end of treatment visit and 12 week Follow-up visit 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 visit and 12 week Follow-up visit. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Section 12.1 (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.

5.5.4 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.

In addition, frequency counts of clinically notable vital signs will be summarized by treatment group. Table 3 presents the clinical notable ranges.

Table 3. Clinical Notable Ranges for Vital Signs

Vital Sign	Criterion for Low	Criterion for High
Pulse (bpm)	< 40	> 120
Temperature (°C)	< 36	> 38
Weight (kg)	< 45	> 100
Systolic BP	< 90	> 160
Diastolic BP	< 50	> 100

Weight increase (>=7%) and weight decrease (>=7%) will be summarized by visit and treatment group.

5.5.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment visit and 12 week Follow-up visit.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in corrected QT interval calculated using Fridericia's formula (QTcF) interval during the treatment period will be summarized. Clinically abnormal ECG results in QTcF interval will be categorized as follows:

Absolute QTcF interval prolongation:

- QTcF interval >450 msec
- QTcF interval >480 msec
- QTcF interval >500 msec

Change from baseline in QTcF interval:

- QTcF interval increases from baseline >30 msec
- QTcF interval increases from baseline >60 msec

Combined:

- QTcF interval >450 msec and QTcF interval increases from baseline >60 msec

5.5.6 Other Safety Analyses

As for Safety magnetic resonance imaging (MRI), findings about vasogenic edema and other abnormalities will be summarized by treatment group using frequencies (number and percentage of subjects). Shift tables will present changes from baseline in white matter disease to each visit and the end of treatment visit and 12 week Follow-up visit by treatment group. Descriptive statistics for total number of microhemorrages will be presented by visit and treatment group.

The Columbia - Suicide Severity Rating Scale (C-SSRS) responses will be mapped to Columbia-classification algorithm of suicide assessment (C-CASA). The incidence of new or worsening suicidal ideation or suicidal behavior will be summarized by treatment group. Categorical variables will be summarized by number (percentage) of subjects. The clinical assessment of suicidal thinking and behavior will be summarized by visit and treatment group.

Additional information on AEs of possible drug abuse potential will be listed. Sleep/Dream questionnaire will be summarized by treatment group.

Cognitive decline will be assessed as a safety assessment, in addition to efficacy assessments. In addition, a greater than 8 point decrease in ADAS-cog word recall score from previous visit triggers an ADAS-cog RCI Alert. ADAS-cog word recall score is calculated by the summation of the words recalled from Word Recall Trial 1, Word Recall Trial 2, Word Recall Trial3, and Delayed Word Recall (Range: 0-40). The number of subjects with ADAS-cog RCI Alert triggered will be summarized by visit and treatment group.

Dermatology findings will be summarized by visit and treatment group.

Neurological examination will be summarized by visit and treatment group.

5.6 Pharmacokinetic, Pharmacodynamic, and PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Pharmacokinetic Analyses

The PK Analysis Set will be used for the summaries of elenbecestat plasma and CSF concentrations.

Pharmacokinetic - Pharmacodynamic Analyses

The PK/PD relationship between CSF biomarker levels, and plasma PK parameters or CSF concentrations of elenbecestat will be explored graphically if a trend in biomarkers with time of treatment is noted

Additionally, the relationship between various PK parameters (eg, C_{max}) or CSF concentrations of elenbecestat and CDR scores (CDR-SB, CDR global score, and CDR Memory Box score) at 24 months (including both absolute score and the change from baseline), and the relationship between various PK exposure parameters or CSF concentrations of elenbecestat and the change

from Baseline for 24 months in ADAS-cog$_{14}$, and the MMSE, will be explored graphically if deemed necessary and only in case of a trend with time of treatment.

5.7 OTHER ANALYSES

No other analyses are planned.

6 INTERIM ANALYSIS

There is no interim analysis of efficacy, but there will be a futility analysis 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.

7 CHANGES IN THE PLANNED ANALYSES

The following analyses will be added because they were focused on DSMB analyses.

- ADAS-cog$_{11}$
- TEAE by SOC/PT based on FDA-defined cognitive PTs
- Abnormal body weight change
- Summary of ADAS-cog RCI Alert Triggered by visit
- Subgroup analysis for very mild subjects defined as baseline CDR-SB≤1.5 and baseline MMSE≥27

The definition of time to worsening of CDR score by 24 months will be modified to use the date of second worsening instead of the date of first worsening in order to focus on sustained worsening.

The analyses to evaluate change from last dose will be added in CDR-SB, ADCOMS, ADAS-cog$_{11}$, ADAS-cog$_{14}$, MMSE, and ADAS-cog$_{14}$ Word List (immediate recall and delayed recall) instead of the analysis for 27 month in CDR-SB.

The following analyses will be conducted as one of sensitivity analyses instead of MMRM by censoring the data after change in concomitant AD medications to minimize the impact not only change in concomitant AD medications but also treatment discontinuation.

- MMRM by censoring the data after intercurrent events (i.e., treatment discontinuation or change in concomitant AD medications)

Several analyses for TEAEs relating to abnormal dreams, nightmares, or sleep terror and TEAEs of clinical interest will be added to evaluate safety profile more.

The following analyses will be removed from the planned analyses because there is a smaller sample size than originally planned.

- Analysis for amyloid PET SUVR, other biomarker endpoints, and exploratory endpoints by study level
- Analysis for CSF Aβ(1-x), CSF Aβ(1-42), and CSF Aβ(1-40) except summary statistics
- Statistical analysis for EQ-5D, QoL-AD, and Zarit's Burden Interview to compare elenbecestat 50 mg versus placebo
- Analysis for OLE data except specified in this SAP

The analyses for tau PET and CSF will be modified to include the assessments collected at early discontinuation visit as much as possible.

The following analyses will be reported separately from the CSR.

- Analysis for functional magnetic resonance imaging (fMRI)

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

8.1 DEFINITION OF BASELINE

The baseline value for efficacy, biomarker and safety will be defined as data collected prior to and/or on the date of first dose, usually the same day as the Day 1 (Visit 2). If there is more than one value on or before Day 1, the value closest to and prior to (including on) the date of first dose will be used as the baseline value.

8.2 DEFINITION OF VISIT WINDOWS

The protocol specified visits/weeks and corresponding time windows used for visit-wise analyses are presented in terms of days relative to the first dose.

Different assessment may have different visit schedule. A general rule for determining a time window for each scheduled visit is to split the two consecutive scheduled visits in the middle point of the two consecutive visits. For example, the time window for visit X is from the middle point between visit (X-1) and X (exclusive) to the middle point between visit X and (X+1) (inclusive). Table 4 shows the case in primary endpoint, as example. The details for other efficacy/biomarker/safety endpoints will be specified in the programming specification.

Table 4. Visit Windows for Primary Endpoint

Analysis visit	Target visit day	Analysis visit window
Baseline	1	The value closest to and prior to (including on) the date of first dose
Week 13 Day 85	85	[43, 134]
Week 27 Day 183	183	[135, 228]
Week 40 Day 274	274	[229, 319]
Week 53 Day 365	365	[320, 410]
Week 66 Day 456	456	[411, 501]
Week 79 Day 547	547	[502, 592]
Week 92 Day 638	638	[593, 683]
Week 105 Day 729	729	[684, 753]

In addition, the following visits will be assigned separately (for efficacy/safety endpoints) if last dose date is known

- Last on treatment: the last post-baseline assessment on or before last dose date. [except EQ-5D/QOL-AD/Zarit's Burden Interview/C-SSRS]

- End of treatment: the earliest assessment on or after last dose date and before last dose date + 56 days (inclusive) [except C-SSRS]

- 12 week Follow-up visit: the closest assessment to last dose date + 84 days after last dose date, but after last dose date + 57 days (inclusive) [except EQ-5D/QOL-AD/Zarit's Burden Interview/C-SSRS]

For efficacy endpoints, the assessments at early discontinuation from study drug, follow-up visits, clinical assessments at 12 and 24 months, unscheduled visits will be assigned to analysis visit using the same visit window rule.

For safety endpoints, the assessments after last dose date + 8 days (inclusive) will not be included in the visit-wise analyses except specific visit described above (the analysis flag should not be "Y"). If last dose date is missing, the assessment at early discontinuation from study drug, follow-up visits and unscheduled visits on or after early discontinuation from study drug or follow-up visits will not be included in the visit-wise analyses.

For biomarker endpoints, the following allowance after last dose date will be used. The assessments out of each allowance will not be included in the visit-wise analyses.

- Amyloid PET: last dose days + 28 days (inclusive)

- Tau PET: no limitation (all assessments will be included)

- CSF Ab(1-x), Ab(1-40), Ab(1-42): last dose days + 5 days (inclusive)_

- Plasma Ab(1-x): last dose days + 5 days (inclusive)

- CSF total tau, p-tau, NFL, neurogranin: no limitation (all assessments will be included)

- Plasma NFL: last dose days + 28 days (inclusive)

- vMRI: no limitation (all assessments will be included)

If last dose date is missing, the assessment at early discontinuation from study drug, follow-up visits and unscheduled visits on or after early discontinuation from study drug or follow-up visits will not be included in the visit-wise analyses for amyloid PET, CSF Ab(1-x), Ab(1-40), Ab(1-42), plasma Ab(1-x), and plasma NFL.

If there are multiple assessments for one analysis visit, the following rules will be applied in order to select one assessment.

1. Pick the closest assessment to the target day

2. Pick the assessment at scheduled visit than unscheduled visit

3. Pick the earliest assessment within the same visit (day)

8.3 DEFINITION OF DURATION OF TREATMENT AND DURATION OF EXPOSURE

The duration of treatment will be calculated using the following equation.

- Duration of treatment = date of last dose of study drug – date of first dose of study drug + 1

The duration of exposure will be calculated using the following equation.

- Duration of exposure = date of last dose of study drug – date of first dose of study drug + 1

If drug interruption occurs, then the drug interruption duration will be subtracted to calculate duration of exposure. For both duration, if the date of last dose of study drug is missing, the date of early discontinuation from study drug will be used instead. If the date of early discontinuation from study drug is also missing, the date of completion or discontinuation will be used instead.

8.4 DEFINITION OF CENSORING RULE FOR CONCOMITANT AD MEDICATIONS

For subjects who start a new AD medication (AChEIs and/or memantine) and were not on an AD medication at randomization, a flag will be set to "Yes" at the visit where the AD medication started and carry forward for all subsequent visits. For subjects who were on an AD medication at the time of randomization and a dose adjustment (increase/decrease/stop) to the AD medication is performed after randomization, a flag will be set to "Yes" at the visit of the dose adjustment and carry forward for all subsequent visits.

For the sensitivity analyses described in Section 5.4.1, the separate analysis flag applying the visit window rule in Section 7.2 after excluding the assessments flagged as "Yes" or after last dose date will be prepared in the datasets.

8.5 ALGORITHMS FOR EFFICACY PARAMETERS

This section describes the algorithms and missing data handling procedure to derive the totals scores for the efficacy parameters: CDR-SB, ADCOMS, ADAS-Cog$_{11}$, ADAS-Cog$_{14}$, MMSE, FAQ, ADAS-cog$_{14}$ Word list, and NPI-10.

CDR-SB: The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant 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 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. If any domain has missing data then the CDR-SB will be missing.

ADCOMS: The derived ADCOMS is a weighted linear combination of 12 items from the three existing 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, which have been selected from the clinical scales, the ADAS-cog, the MMSE, and the CDR. The names of these item and the corresponding scale names are described in Table 5.

Table 5: Predictive Variables for the Derived 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.

The derived composite score will be calculated from these predictive variables according to the formula:
Derived composite Score =A4 *0.00847483 + A7 *0.017088 + A8 *0.003732761 + A11*0.016211 + (5-M1)*0.041567 + (1-M7)*0.038238 + C1*0.054321+ C2*0.1091+ C3*0.089039 + C4*0.069493 + C5*0.058724 + C6*0.078152.

The maximum derived composite score is achieved when each item is assigned the maximum score. This maximum composite score is 1.97. The range of this new composite score is therefore between 0 and 1.97.

If any subscale has missing data then the ADCOMS will be missing. ADAS-cog, MMSE and CDR assessed at same CRF visit are used to derive the composite score even they are assessed in separate date.

ADAS-cog$_{11}$ and ADAS-Cog$_{14}$: The ADAS-cog is the most widely used cognitive scale in AD clinical studies. The 14-item version (as shown in Table 6) is considered more sensitive for less

impaired populations such as MCI/Prodromal and mild AD subjects. ADAS-cog$_{11}$ consists of 11-item (Delayed Word Recall, Executive Function, and Number Cancellation are excluded). If any item score is missing then the Total Score is missing.

Table 6. ADAS-cog$_{14}$ Items and Algorithm for Derivation of Item Scores and Total Score

Item	Algorithm	Handling Missing Data	Score Range
1. Word Recall	Total the number of "No" responses for each trial. The subscore is the sum the scores from trials 1, 2, and 3, divided by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 10
2. Commands	Total the number of "No" responses from the 5 tasks	If any task is missing then the subscore is missing	0 to 5
3. Constructional Praxis	Count the number of "No" responses. The subscore is 0 = all 4 drawings correct 1= 1 figure drawn incorrectly 2= 2 figures drawn incorrectly 3= 3 figures drawn incorrectly 4= 4 figures drawn incorrectly 5= no figures drawn, scribbles, parts of forms	If any task is missing then the subscore is missing	0 to 5
4. Delayed Word-Recall	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 10
5. Naming Objects / Fingers	Total the number of "No" responses. The subscore is 0= 0-2 "no" responses 1= 3-5 "no" responses 2= 6-8 "no" responses 3= 9-11 "no" responses 4= 12-14 "no" responses 5= 15-17 "no" responses	If any response is missing then subscore is missing	0 to 5
6. Ideational Praxis	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 5
7. Orientation	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 8
8. Word Recognition	For each trial, total the number of "1" responses. If the total is 12 or less, then the trial score = total. If the total is > 12 then trial score=12. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 12
9. Remembering Test Instructions	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5

10. Comprehension	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
11. Word Finding Difficulty	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
12. Spoken Language Ability	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
13. Executive Function (Maze)	The subscore is based on the total number of seconds to complete the task and/or whenever the task was stopped due to 2 errors being made, as follows; 0 = 0-30 seconds 1 = 31-60 seconds 2 = 61 – 90 seconds 3 = 91 – 120 seconds 4 = 121-239 seconds 5 = 240 seconds or at least 2 errors	If the response is missing then the subscore is missing	0 to 5
14. Number Cancellation	Adjusted Score = Total # correct targets crossed off minus Total # incorrect targets crossed off minus Total # times reminded of task. Then use Adjusted Score to determine the subscore as follows; Adjusted Score = Subscore ≥23 = 0 18-22 = 1 13-17 = 2 9-12 = 3 5-8 = 4 ≤4 = 5	If any component of the adjusted score is missing then the subscore is missing	0 to 5
Total Score	Total Score = sum of the subscores above	If any subscore is missing then Total Score is missing	0 to 90

MMSE: 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. MMSE is composed of 30 questions group into domains. For each of the MMSE domains add the correct responses. If a domain has missing data then the domain is missing. From the domains, one can compute the six items as show in Table 7. If any domain is missing then the item is missing. The MMSE Total Score (range 0 to 30) = sum of the six items. If any item score is missing then the Total Score is missing.

Table 7. MMSE Domains and Items

Domain	Score Range	Item	Score Range
1. Orientation to Time	0 to 5	1. Orientation to Time	0 to 5
2. Orientation to Place	0 to 5	2. Orientation to Place	0 to 5
3. Registration	0 to 3	3. Registration	0 to 3
4. Attention and Calculation[a]	0 to 5	4. Attention and Calculation	0 to 5
5. Recall	0 to 3	5. Recall	0 to 3
6. Naming	0 to 2	6. Language (Sum of Naming, Repetition, Comprehension, Reading, Writing, and Drawing)	0 to 9
7. Repetition	0 to 1		
8. Comprehension	0 to 3		
9. Reading	0 to 1		
10. Writing	0 to 1		
11. Drawing	0 to 1		
		Total Score	**0 to 30**

[a] Spell WORD Forward, then Backward score is only use if Attention and Calculation score is not available

FAQ: The FAQ is composed of 10 activities. Each activity is rated as 0 = Normal, 1 = Has difficulty but does by self, 2 = Requires assistance, 3 = Dependent, 8 = Not Applicable. The Total Score is the sum of the 10 activity. If any activity is missing then the Total Score is missing. Activities marked as "Not Applicable", are not use in the computation of the Total Score. However, in order to account for "Not Applicable" activity(s), the Total Score is weighted as follows;

Total Score = Total Score x 30 / (30 minus 3 times the number of activities marked "Not Applicable")

ADAS-cog$_{14}$ Word list: The summation of "1. Word Recall" and "4. Delayed Word-Recall" from ADAS-cog$_{14}$ Items. The score range is 0 to 20. If any word recall score is missing then word list score is missing.

NPI-10: If NPI-12 is available instead of NPI-10, each sub scale and total score for NPI-10 will be derived from NPI-12 sub scales. If any sub scale is missing then total score (distress or domain score) is missing.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

The following sample SAS statement provides the framework for the MI method:

CONVERT DATASET INTO MONOTONE MISSING DATA PATTERN (IMPUTING ARBITRARY MISSING DATA):

PROC MI data=<dataset> nimpute=1000 seed=2609 out=<dataset1>;

```
  VAR base visit1 … visit8;
  MCMC chain=multiple impute=monotone;
  EM maxiter=15000;
  BY trt01pn;
RUN;
```

IMPUTE MISSING VALUES:

```
PROC MI data=<dataset1> nimpute=1 seed=2609 out=<dataset2>;
  CLASS trt01pn;
  MONOTONE regression (/details);
  VAR trt01pn base visit 1 … visit8;
  BY _imputation_;
RUN;
```

PERFORMING ANCOVA:

```
PROC MIXED data=<dataset2>;
  CLASS trt01pn clindem curadmed apoe4st region;
  MODEL chg = base trt01pn clindem curadmed apoe4st region;
  LSMEANS trt01pn / DIFF CL;
  BY _imputation_;
  ODS output diffs=<dataset3>;
RUN;
```

COMBINE RESULTS:

```
PROC MIANALYZE data=<dataset3>;
  MODELEFFECTS estimate;
  STDERR stderr;
RUN;
```

10 STATISTICAL SOFTWARE

All statistical analyses will be performed by Eisai Inc., using SAS Version 9.4 or later.

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. Rubin D.B. Multiple Imputation for Nonresponse in Surveys. John Wiley & Sons. 1987.
2. Dhadda, S., Swanson, C., Scott, D., Zhang, Y., Zhao, J., Wang, J., Luthman, J., Kramer, L. Baseline Florbetapir Amyloid PET Standard Uptake Value Ratio (SUVR) Predicts Clinical Stage in Pre-clinical Alzheimer's Disease (AD) and Mild Cognitive Impairment (MCI). 2018. AAIC.
3. Adamczuk, K., Sampat, M., Bracoud, L., Runkle, M., Gorman, B., Suhy, J., Scott, D. Centiloid Scale in Practice: Effect of Different SUVr Reference Regions and Comparison of Centiloid Cut-Offs. 2019. AAIC.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table 8 of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Table 8. 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

	Grade 1	Grade 2	Grade 3	Grade 4
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 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).

STATISTICAL ANALYSIS PLAN

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
Date:	06 Feb 2017, (V3.0, Amendment 02)

SIGNATURE PAGE

Author:

PPD

Neurology Business Group, Eisai

[electronic signature in eDMS]
Signature

Date: _____

Approval

Biostatistics:

PPD

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Study Director:

PPD Neuroscience PCU

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[electronic signature in eDMS]
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Date: _____

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AE	adverse event
AChEI	Acetylcholinesterase inhibitors
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoE	apolipoprotein E
BMI	body mass index
CBB	Cogstate Brief Battery
CC	Complete cases
C-CASA	Columbia- classification algorithm of suicide assessment
CI	confidence interval
CDR	Clinical Dementia Rating
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia - Suicide Severity Rating Scale
DMC	data monitoring committee
DSMB	data safety monitoring board
EAD	Early Alzheimer's Disease
ECG	electrocardiogram
EQ-5D	EuroQol-5 Dimensions
FAQ	Functional Activities Questionnaire
FAS	full analysis set
fMRI	functional magnetic resonance imaging
IA	Interim Analysis
ISLT	International Shopping List Task
ITT	intent to treat
LS	least squares
MAR	missing at random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMSE	Mini Mental State Examination
MMRM	mixed-effects models for repeated measures
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography

PD	pharmacodynamic
PG	pharmacogenomic
PK	pharmacokinetic
PP	per protocol
PT	preferred term
QTc	corrected QT interval
QOL-AD	Quality of Life in Alzheimer's Disease
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SE	standard error
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory
TLG	tables, listings, and graphs
vMRI	volumetric magnetic resonance imaging
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study E2609-G000-301. This SAP is based on the protocol amendment 02 (06FEB2017, v3.0).

3.1 STUDY OBJECTIVES

3.1.1 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)

3.1.2 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

3.1.3 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

3.1.4 Exploratory Objectives

- To explore the relationship between elenbecestat (E2609)'s exposure (in CSF, plasma), PD, efficacy, and safety endpoints (eg, immune function), as deemed appropriate

- 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

3.2 OVERALL STUDY DESIGN AND PLAN

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). 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 the 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 months Prerandomization Phase, followed by 24 months of treatment and a 3 month Follow-Up Phase).

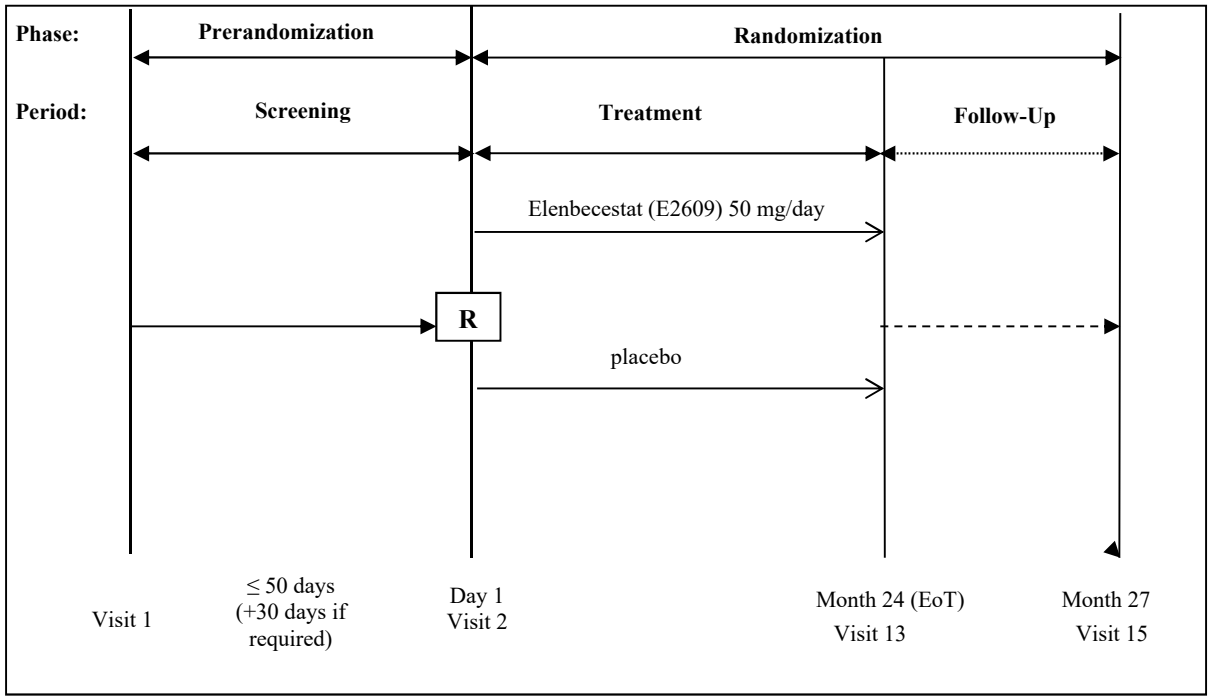
The study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers.

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.

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.

Figure 1 Study Design of E2609-G000-301



Elebbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

4 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.

5 STATISTICAL METHODS

Statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. A snapshot of the safety data will be obtained and released for analysis for the DSMB. A copy of this snapshot will be archived. 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.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

A statistical analysis report or topline report will be produced after database lock, which consists mainly of key efficacy and safety results.

The efficacy and safety results in Chinese subjects will be summarized to fulfill the requirement of CFDA.

5.1 STUDY ENDPOINTS

6.1.1 PRIMARY ENDPOINT

- Change from baseline in the CDR-SB at 24 months

6.1.2 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

6.1.3 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

6.1.4 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

5.2 STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

The definitions of the analysis data sets are:

- 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. Safety Analysis Set will be used in the statistical analyses for safety. In the event that a subject received study drug different from the one to which this subject was randomized, the subject's safety data will be analyzed "as treated."
- 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. FAS will be used for all the efficacy and biomarker analyses.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. PPS will be used to conduct a sensitivity analysis of the primary efficacy endpoint. The criteria for exclusion from PPS are listed below:
    - Violation of any of the following inclusion criteria:
        - MMSE score equal to or greater than 24
        - CDR global score of 0.5
        - CDR Memory Box score of 0.5 or greater
        - Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT
        - Positive biomarker for brain amyloid pathology as indicated by PET assessment of amyloid imaging agent uptake into brain and/or CSF assessment of Aβ(1-42)
    - Poor study drug compliance: compliance up to last dose of study drug <80%
- 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.

5.2.2 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.

5.2.3 Protocol Deviations

A listing of subjects with protocol deviations will be provided by subject along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock.

5.2.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the Safety Analysis set and FAS will be summarized by treatment group using descriptive statistics.

Continuous demographic and baseline variables include: age (years), baseline height (cm) and weight (kg), CDR-SB score, ADAS-cog_{14}, ADAS-cog_{14} Word List, MMSE, ISLT, FAQ, years since onset of cognitive impairment symptoms, and years since disease diagnosis.

Categorical variables include: age group (<65, ≥65 - <80, and ≥80), sex, race, ethnicity, region, concurrent treatment with AChEIs or memantine (no, yes), clinical dementia (no, yes), *ApoE4* genotype, and CDR Memory Box score.

MEDICAL HISTORY

The medical history verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database. The number (percent) of subjects will be presented by preferred term and treatment group.

5.2.5 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). 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.

Prior and concomitant therapies for AD and those for non-AD will be summarized separately.

5.2.6 Treatment Compliance

Treatment compliance (%) will be calculated for Safety Analysis set as follows:

$$\frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned}}{\text{Planned Total number of tablets to be taken}} * 100\%$$

Compliance will be calculated in two ways: compliance up to the last dose (day) of study drug, and overall compliance. Overall compliance will be calculated as the 24-month compliance by assuming each subject has been followed through 24 months in the study; a subject will be considered to take no study drug after study drug discontinuation until the end of 24 months.

Treatment compliance will be summarized using descriptive statistics by treatment group. Subjects will also be categorized by compliance criteria <60%, 60%-80%, 80%-100%, and >100%.

5.3 DATA ANALYSIS GENERAL CONSIDERATIONS

5.3.1 Pooling of Centers

This study has used region as a stratification factor for randomization, therefore, there is no plan to pool any other type of centers or sites.

The regions and corresponding countries that might be included and are grouped together in a particular region are:

1. North America: US, and Canada

2. Western Europe (including Oceania region): Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, New Zealand, Portugal, Slovakia, Spain, Sweden, Switzerland, and United Kingdom

3. Eastern Europe: Bulgaria, Croatia, Lithuania, Poland, Romania, Russian Federation, and Ukraine

4. Japan

5. China

6. Other Asian countries/regions: Hong Kong, Japan, South Korea, Singapore, and Taiwan

7. South America: Argentina, Brazil, Chile, and Mexico

5.3.2 Adjustments for Covariates of Interest

The primary, secondary, and exploratory efficacy endpoints will include the stratification variables (region, concurrent treatment with AChEIs or memantine, clinical dementia) and baseline value of the endpoint (if applicable) as covariates. In addition, demographic and baseline characteristics covariates of interest will be evaluated in the statistical models, which include:

1. Age treated as continuous and as categorical (<65, ≥65 - <80, and ≥80 years)
2. Sex
3. Race
4. Ethnicity
5. *ApoE4* genotype

5.3.3 Multiple Comparisons/Multiplicity

The primary and secondary endpoints 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 hierarchical order for these endpoints is:

1. Change from baseline in the CDR-SB at 24 months (primary endpoint)

2. 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)

3. Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

4. The rate of change over time (mean slope) based on CDR-SB score over 24 months

5. Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months

6. Change from baseline in ADAS-cog_{14} Word List (immediate recall and delayed recall) at 24 months

7. Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)

Analyses on biomarker and exploratory endpoints will be conducted without adjustment for multiplicity.

5.3.4 Examination of Subgroups

Subgroup analysis will be performed for the primary and secondary efficacy endpoints, and also biomarker endpoints. The subgroups include:

- age at baseline (<65, ≥65 - <80, and ≥80 years)
- sex
- race
- ethnicity
- region (section 6.3.1)
- clinical dementia (no, yes)
- concurrent treatment with AChEIs or memantine (no, yes)

- *ApoE4* genotype
- baseline CDR Memory Box score

Forest plot will be generated to visually display the treatment difference with 95% confidence interval, no significance tests will be performed in the subgroups.

5.3.5 Handling of Missing Data

Clinical Assessment

If any item is missing within the CDR, ADAS-cog$_{14}$, MMSE, and FAQ, then their respective total scores will be missing.

CSF Biomarkers

- If any amyloid β Aβ42 measurement is "<LLOQ", then the measurement will be imputed by LLOQ 125 pg/mL.
- If any p-Tau 181 measurement is "<LLOQ", then the measurement will be imputed by LLOQ 16 pg/mL.
- If any Tau measurement is "<LLOQ", then the measurement will be imputed by LLOQ 75 pg/mL.

Others

Adverse events with missing severity will be assigned the highest severity. Adverse events with missing relationship will be assigned the highest relationship.

5.3.6 Other Considerations

Not Applicable.

5.4 EFFICACY ANALYSES

5.4.1 Primary Efficacy Analysis

Regarding the primary endpoint, 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 based on the intent to treat (ITT) philosophy without regard to adherence to treatment. The analysis will be performed by 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 least squares (LS) means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

Sensitivity Analyses

1). An MMRM analysis will be performed on the PPS.

2). To minimize the impact of change in concomitant AD medications, an MMRM analysis will be conducted on both FAS and PPS, by censoring the data after initiation of new AD medications (AChEI or memantine) and/or change in dose of current AD medications.

3). An analysis of covariance (ANCOVA) model will be used after multiple imputation to evaluate the impact of missing data in both FAS and PPS. The model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Analysis for Chinese Subjects

LS mean and 95% CI for the difference between treatment groups as well as LS means and SE for each treatment group will be estimated using MMRM similar to the primary analysis. The treatment effect in Chinese subjects will be examined against the overall population using a forest plot.

5.4.2 Secondary Efficacy Analyses

The secondary endpoints 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 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

Time to worsening of CDR scores by 24 months

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using a 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 - increase from baseline by at least 0.5 points on the global CDR score, 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 by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

This endpoint will be analyzed on the FAS using a 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 in clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at baseline is defined as time from randomization to conversion to dementia in clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia will be censored at the date of last dementia diagnosis.

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 rate of change over time (mean slope) based on CDR-SB score over 24 months

The rate of change over time (mean slope) for the change from baseline in 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.

Other continuous endpoints

The other continuous secondary efficacy endpoints will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg versus placebo on the FAS, using baseline value corresponding to the response variable in the model. These endpoints include:

- 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

With regard to the change from baseline in ADAS-cog$_{14}$ Word List, it includes the immediate and delayed recall tasks, their scores will be part of the ADAS-cog$_{14}$ assessment (Item 1 and 4).

5.4.3 Biomarker Endpoints

The biomarker endpoints are changes from baseline in:

- Amyloid PET SUVR composite at 24 months for brain amyloid levels
- CSF biomarkers t-tau and p-tau at 24 months
- CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Total hippocampal volume at 24 months using vMRI
- Preservation of connectivity on fMRI at 24 months

The analysis of the above endpoints will be performed by using MMRM or ANCOVA model, 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.

The relationship between clinical changes (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in 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 of clinical scale as a covariate, randomization stratification variables and treatment group as factors, and other terms as appropriate.

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using ANCOVA model with changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

5.4.4 Exploratory Endpoints

The exploratory endpoints 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

Time to change of concomitant AD treatment will be analyzed similarly as that used for the time to conversion to dementia based on clinical diagnosis, as described in the 2nd endpoints. 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 as that used for the proportion of subjects with dementia diagnosis at 24 months, as described in section 6.4.2.

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 as that used for the rate of change over time (mean slope) for the change from baseline in CDR-SB, as described in section 6.4.2.

Analysis of the change from baseline exploratory endpoints will be performed to compare elenbecestat (E2609) versus placebo by using MMRM or ANCOVA model. For each of them, the treatment effect of elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. These endpoints include:

- 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

5.5 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.

5.5.1 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.

5.5.2 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, concurrent treatment with AChEIs or memantine (no, yes), and clinical dementia (no, yes).

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.

5.5.3 Laboratory Values

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters, 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 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.

Section 12.1 (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.

5.5.4 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.

In addition, frequency counts of clinically notable vital signs will be summarized by treatment group. Table 3 presents the clinical notable ranges.

Table 1. Clinical Notable Ranges for Vital Signs

Vital Sign	Criterion for Low	Criterion for High
Pulse (bpm)	< 50	> 100
Temperature (°C)	< 36	> 38
Weight (kg)	< 45	> 100
Systolic BP	< 90	> 160
Diastolic BP	< 50	> 100

5.5.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec

- QTc interval increases from baseline >60 msec

5.5.6 C-SSRS

The C-SSRS responses will be mapped to C-CASA. The incidence of new or worsening suicidal ideation or suicidal behavior will be summarized by treatment group. Continuous variables will be summarized by descriptive statistics; number of subjects, mean, standard deviation, median, minimum, and maximum and categorical variables by number (percentage) of subjects.

5.5.7 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.

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy. 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.

5.6 Pharmacokinetic, Pharmacodynamic, and PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Pharmacokinetic Analyses

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.

Pharmacokinetic - Pharmacodynamic Analyses

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 scores (CDR-SB, CDR global score, and CDR Memory Box score) at 24 months (including both absolute score and the change from baseline), 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.

Details of further analyses of pharmacokinetic/pharmacodynamic data will be described in a separate PK/PD analysis plan.

5.7 OTHER ANALYSES

No other analyses are planned.

6 INTERIM ANALYSIS

There is no interim analysis of efficacy, but there will be a futility analysis 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.

7 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1 DEFINITION OF BASELINE

The baseline value for efficacy, biomarker and safety will be defined as data collected prior to and/or on the date of first dose, usually the same day as the Day 1 (Visit 2). If there is more than one value on or before Day 1, the value closest to and prior to (including on) the date of first dose will be used as the baseline value.

7.2 ALGORITHMS FOR EFFICACY PARAMETERS

This section describes the algorithms and missing data handling procedure to derive the totals scores for the efficacy parameters: CDR, ADAS-Cog_{14}., MMSE, and FAQ.

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant 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 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.

ADAS-cog_{14}: The ADAS-cog is the most widely used cognitive scale in AD clinical studies. The 14-item version (as shown in Table 4) is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects.

Table 2. ADAS-cog_{14} Items and Algorithm for Derivation of Item Scores and Total Score

Item	Algorithm	Handling Missing Data	Score Range
1. Word Recall	Total the number of "No" responses for each trial. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 10
2. Commands	Total the number of "No" responses from the 5 tasks	If any task is missing then the subscore is missing	0 to 5
3. Constructional Praxis	Count the number of "No" responses. The subscore is	If any task is missing then the subscore is missing	0 to 5

	0 = all 4 drawings correct 1= 1 figure drawn incorrectly 2= 2 figures drawn incorrectly 3= 3 figures drawn incorrectly 4= 4 figures drawn incorrectly 5= no figures drawn, scribbles, parts of forms		
4. Delayed Word-Recall	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 10
5. Naming Objects / Fingers	Total the number of "No" responses. The subscore is 0= 0-2 "no" responses 1= 3-5 "no" responses 2= 6-8 "no" responses 3= 9-11 "no" responses 4= 12-14 "no" responses 5= 15-17 "no" responses	If any response is missing then subscore is missing	0 to 5
6. Ideational Praxis	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 5
7. Orientation	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 8
8. Word Recognition	For each trial, total the number of "1" responses. If the total is 12 or less, then the trial score = total. If the total is > 12 then trial score=12. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 12
9. Remembering Test Instructions	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
10. Comprehension	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
11. Word Finding Difficulty	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
12. Spoken Language Ability	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
13. Executive Function (Maze)	The subscore is based on the total number of seconds to complete the task and/or whenever the task was stopped due to 2 errors being made, as follows; 0 = 0-30 seconds 1 = 31-60 seconds 2 = 61 – 90 seconds 3 = 91 – 120 seconds 4 = 121-239 seconds	If the response is missing then the subscore is missing	0 to 5

	5 = 240 seconds or at least 2 errors		
14. Number Cancellation	Adjusted Score = Total # correct targets crossed off minus Total # incorrect targets crossed off minus Total # times reminded of task. Then use Adjusted Score to determine the subscore as follows; Adjusted Score = Subscore ≥23 = 0 18-22 = 1 13-17 = 2 9-12 = 3 5-8 = 4 ≤4 = 5	If any component of the adjusted score is missing then the subscore is missing	0 to 5
Total Score	Total Score = sum of the subscores above	If any subscore is missing then Total Score is missing	0 to 90

MMSE: 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. MMSE is composed of 30 questions group into domains. For each of the MMSE domains add the correct responses. If a domain has missing data then the domain is missing. From the domains, one can compute the six items as show in Table 5. If any domain is missing then the item is missing. The MMSE Total Score (range 0 to 30) = sum of the six items. If any item score is missing then the Total Score is missing.

Table 3. MMSE Domains and Items

Domain	Score Range	Item	Score Range
1. Orientation to Time	0 to 5	1. Orientation to Time	0 to 5
2. Orientation to Place	0 to 5	2. Orientation to Place	0 to 5
3. Registration	0 to 3	3. Registration	0 to 3
4. Attention and Calculation[a]	0 to 5	4. Attention and Calculation	0 to 5
5. Recall	0 to 3	5. Recall	0 to 3
6. Naming	0 to 2	6. Language (Sum of Naming, Repetition, Comprehension, Reading, Writing, and Drawing)	0 to 9
7. Repetition	0 to 1		
8. Comprehension	0 to 3		
9. Reading	0 to 1		
10. Writing	0 to 1		
11. Drawing	0 to 1		
		Total Score	**0 to 30**

[a] Spell WORD Forward, then Backward score is only use if Attention and Calculation score is not available

FAQ: The FAQ is composed of 10 activities. Each activity is rated as 0 = Normal, 1 = Has difficulty but does by self, 2 = Requires assistance, 3 = Dependent, 8 = Not Applicable. The Total Score is the sum of the 10 activity. If any activity is missing then the Total Score is missing. Activities marked as "Not Applicable", are not use in the computation of the Total Score. However, in order to account for "Not Applicable" activity(s), the Total Score is weighted as follows;

Total Score = Total Score x 30 / (30 minus 3 times the number of activities marked "Not Applicable")

8 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

9 STATISTICAL SOFTWARE

All statistical analyses will be performed by Eisai Inc., using SAS Version 9.3.

10 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

11 REFERENCES

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12 APPENDICES

12.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table 7 of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Table 4. 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

	Grade 1	Grade 2	Grade 3	Grade 4
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 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).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Approval	29-Mar-2017 16:59 GMT-04
	Document Originator Approval	29-Mar-2017 17:01 GMT-04
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STATISTICAL ANALYSIS PLAN

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
Date:	06 Feb 2017, (V2.0, Amendment 01)

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1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
AD	Alzheimer's Disease
ADAS-cog	Alzheimer's Disease Assessment Scale – Cognitive Subscale
AE	adverse event
AChEI	Acetylcholinesterase inhibitors
ANCOVA	analysis of covariance
ANOVA	analysis of variance
ApoE	apolipoprotein E
BMI	body mass index
CBB	Cogstate Brief Battery
CC	Complete cases
C-CASA	Columbia- classification algorithm of suicide assessment
CI	confidence interval
CDR	Clinical Dementia Rating
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSF	cerebrospinal fluid
CSR	clinical study report
C-SSRS	Columbia - Suicide Severity Rating Scale
DMC	data monitoring committee
DSMB	data safety monitoring board
EAD	Early Alzheimer's Disease
ECG	electrocardiogram
EQ-5D	EuroQol-5 Dimensions
FAQ	Functional Activities Questionnaire
FAS	full analysis set
fMRI	functional magnetic resonance imaging
IA	Interim Analysis
ISLT	International Shopping List Task
ITT	intent to treat
LS	least squares
MAR	missing at random
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MMSE	Mini Mental State Examination
MMRM	mixed-effects models for repeated measures
PBMC	peripheral blood mononuclear cell
PET	positron emission tomography

PD	pharmacodynamic
PG	pharmacogenomic
PK	pharmacokinetic
PP	per protocol
PT	preferred term
QTc	corrected QT interval
QOL-AD	Quality of Life in Alzheimer's Disease
SAE	serious adverse event
SAP	statistical analysis plan
SAS	statistical analysis system
SD	standard deviation
SE	standard error
SI	Système International
SOC	system organ class
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory
TLG	tables, listings, and graphs
vMRI	volumetric magnetic resonance imaging
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for study E2609-G000-302. This SAP is based on the protocol amendment 01 (06FEB2017, v2.0).

3.1 STUDY OBJECTIVES

3.1.1 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)

3.1.2 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

3.1.3 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

3.1.4 Exploratory Objectives

- To explore the relationship between elenbecestat (E2609)'s exposure (in CSF, plasma), PD, efficacy, and safety endpoints (eg, immune function), as deemed appropriate

- 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

3.2 OVERALL STUDY DESIGN AND PLAN

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). 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 the 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 months Prerandomization Phase, followed by 24 months of treatment and a 3 month Follow-Up Phase).

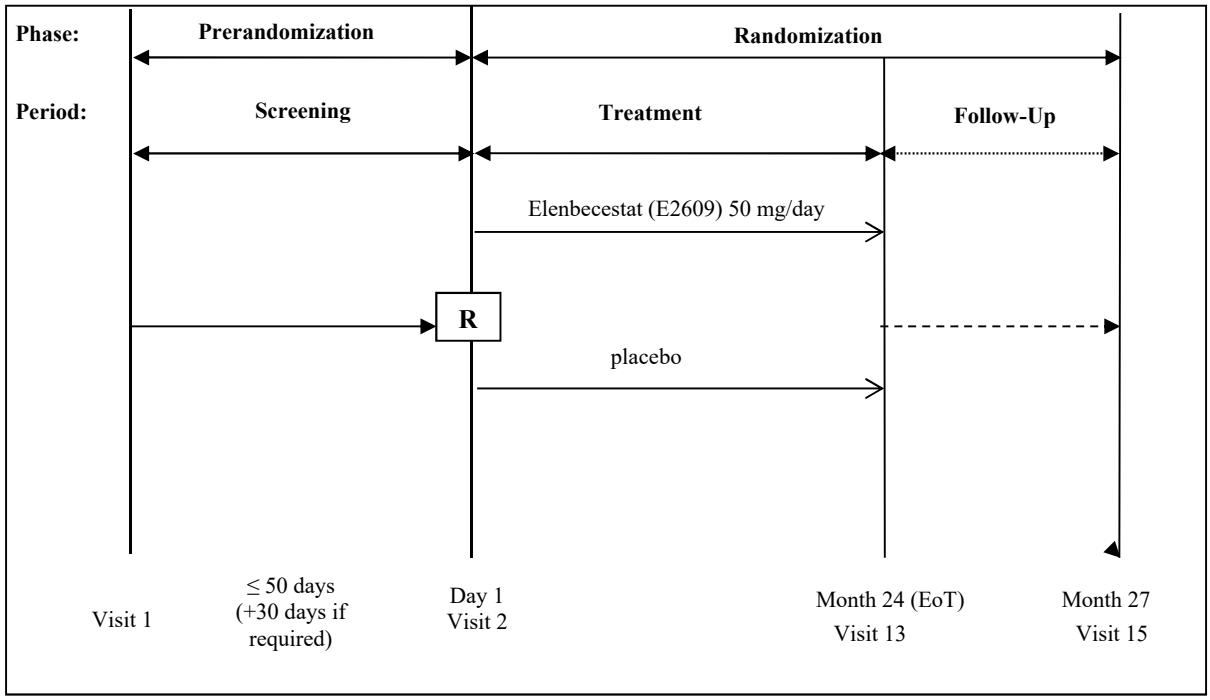
The study will consist of Prerandomization and Randomization Phases. The Prerandomization Phase (up to 50 days, plus an additional window of up to 30 days if required) includes a Screening Visit. Screening assessments/procedures have been organized into 5 distinct tiers.

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.

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.

Figure 1 Study Design of E2609-G000-302



Elebbecestat (E2609) = Test drug, EoT = End of Treatment, R = randomization.

4 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.

5 STATISTICAL METHODS

Statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. A snapshot of the safety data will be obtained and released for analysis for the DSMB. A copy of this snapshot will be archived. 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.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

A statistical analysis report or topline report will be produced after database lock, which consists mainly of key efficacy and safety results.

The efficacy and safety results in Chinese subjects will be summarized to fulfill the requirement of CFDA.

5.1 STUDY ENDPOINTS

6.1.1 PRIMARY ENDPOINT

- Change from baseline in the CDR-SB at 24 months

6.1.2 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

6.1.3 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

6.1.4 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

5.2 STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

The definitions of the analysis data sets are:

- 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. Safety Analysis Set will be used in the statistical analyses for safety. In the event that a subject received study drug different from the one to which this subject was randomized, the subject's safety data will be analyzed "as treated."
- 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. FAS will be used for all the efficacy and biomarker analyses.
- The Per Protocol Analysis Set (PPS) is the subset of subjects in the FAS who sufficiently comply with the protocol. PPS will be used to conduct a sensitivity analysis of the primary efficacy endpoint. The criteria for exclusion from PPS are listed below:
    - Violation of any of the following inclusion criteria:
        - MMSE score equal to or greater than 24
        - CDR global score of 0.5
        - CDR Memory Box score of 0.5 or greater
        - Cognitive impairment of at least 1 SD from age-adjusted norms in total recall or delayed recall on the ISLT
        - Positive biomarker for brain amyloid pathology as indicated by PET assessment of amyloid imaging agent uptake into brain and/or CSF assessment of Aβ(1-42)
    - Poor study drug compliance: compliance up to last dose of study drug <80%
- 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.

5.2.2 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.

5.2.3 Protocol Deviations

A listing of subjects with protocol deviations will be provided by subject along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock.

5.2.4 Demographic and Baseline Characteristics

Demographic and baseline characteristics for the Safety Analysis set and FAS will be summarized by treatment group using descriptive statistics.

Continuous demographic and baseline variables include: age (years), baseline height (cm) and weight (kg), CDR-SB score, ADAS-cog_{14}, ADAS-cog_{14} Word List, MMSE, ISLT, FAQ, years since onset of cognitive impairment symptoms, and years since disease diagnosis.

Categorical variables include: age group (<65, ≥65 - <80, and ≥80), sex, race, ethnicity, region, concurrent treatment with AChEIs or memantine (no, yes), clinical dementia (no, yes), *ApoE4* genotype, and CDR Memory Box score.

MEDICAL HISTORY

The medical history verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database. The number (percent) of subjects will be presented by preferred term and treatment group.

5.2.5 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). 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.

Prior and concomitant therapies for AD and those for non-AD will be summarized separately.

5.2.6 Treatment Compliance

Treatment compliance (%) will be calculated for Safety Analysis set as follows:

$$\frac{\text{Total number of tablets dispensed} - \text{Total number of tablets returned}}{\text{Planned Total number of tablets to be taken}} * 100\%$$

Compliance will be calculated in two ways: compliance up to the last dose (day) of study drug, and overall compliance. Overall compliance will be calculated as the 24-month compliance by assuming each subject has been followed through 24 months in the study; a subject will be considered to take no study drug after study drug discontinuation until the end of 24 months.

Treatment compliance will be summarized using descriptive statistics by treatment group. Subjects will also be categorized by compliance criteria <60%, 60%-80%, 80%-100%, and >100%.

5.3 DATA ANALYSIS GENERAL CONSIDERATIONS

5.3.1 Pooling of Centers

This study has used region as a stratification factor for randomization, therefore, there is no plan to pool any other type of centers or sites.

The regions and corresponding countries that might be included and are grouped together in a particular region are:

1. North America: US, and Canada

2. Western Europe (including Oceania region): Australia, Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Hungary, Ireland, Italy, Netherlands, New Zealand, Portugal, Slovakia, Spain, Sweden, Switzerland, and United Kingdom

3. Eastern Europe: Bulgaria, Croatia, Lithuania, Poland, Romania, Russian Federation, and Ukraine

4. Japan

5. China

6. Other Asian countries/regions: Hong Kong, Japan, South Korea, Singapore, and Taiwan

7. South America: Argentina, Brazil, Chile, and Mexico

5.3.2 Adjustments for Covariates of Interest

The primary, secondary, and exploratory efficacy endpoints will include the stratification variables (region, concurrent treatment with AChEIs or memantine, clinical dementia) and baseline value of the endpoint (if applicable) as covariates. In addition, demographic and baseline characteristics covariates of interest will be evaluated in the statistical models, which include:

1. Age treated as continuous and as categorical (<65, ≥65 - <80, and ≥80 years)
2. Sex
3. Race
4. Ethnicity
5. *ApoE4* genotype

5.3.3 Multiple Comparisons/Multiplicity

The primary and secondary endpoints 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 hierarchical order for these endpoints is:

1. Change from baseline in the CDR-SB at 24 months (primary endpoint)

2. 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)

3. Time to conversion to dementia by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

4. The rate of change over time (mean slope) based on CDR-SB score over 24 months

5. Change from baseline in ADAS-cog_{14}, MMSE, and FAQ at 24 months

6. Change from baseline in ADAS-cog_{14} Word List (immediate recall and delayed recall) at 24 months

7. Change from baseline in CDR-SB at 27 months (ie, 24 months of treatment plus 3 months posttreatment follow-up)

Analyses on biomarker and exploratory endpoints will be conducted without adjustment for multiplicity.

5.3.4 Examination of Subgroups

Subgroup analysis will be performed for the primary and secondary efficacy endpoints, and also biomarker endpoints. The subgroups include:

- age at baseline (<65, ≥65 - <80, and ≥80 years)
- sex
- race
- ethnicity
- region (section 6.3.1)
- clinical dementia (no, yes)
- concurrent treatment with AChEIs or memantine (no, yes)

- *ApoE4* genotype
- baseline CDR Memory Box score

Forest plot will be generated to visually display the treatment difference with 95% confidence interval, no significance tests will be performed in the subgroups.

5.3.5 Handling of Missing Data

Clinical Assessment

If any item is missing within the CDR, ADAS-cog_{14}, MMSE, and FAQ, then their respective total scores will be missing.

CSF Biomarkers

- If any amyloid β Aβ42 measurement is "<LLOQ", then the measurement will be imputed by LLOQ 125 pg/mL.
- If any p-Tau 181 measurement is "<LLOQ", then the measurement will be imputed by LLOQ 16 pg/mL.
- If any Tau measurement is "<LLOQ", then the measurement will be imputed by LLOQ 75 pg/mL.

Others

Adverse events with missing severity will be assigned the highest severity. Adverse events with missing relationship will be assigned the highest relationship.

5.3.6 Other Considerations

Not Applicable.

5.4 EFFICACY ANALYSES

5.4.1 Primary Efficacy Analysis

Regarding the primary endpoint, 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 based on the intent to treat (ITT) philosophy without regard to adherence to treatment. The analysis will be performed by 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 least squares (LS) means and difference in LS means between elenbecestat (E2609) treatment group and placebo, and corresponding 95% CI will be presented.

Sensitivity Analyses

1). An MMRM analysis will be performed on the PPS.

2). To minimize the impact of change in concomitant AD medications, an MMRM analysis will be conducted on both FAS and PPS, by censoring the data after initiation of new AD medications (AChEI or memantine) and/or change in dose of current AD medications.

3). An analysis of covariance (ANCOVA) model will be used after multiple imputation to evaluate the impact of missing data in both FAS and PPS. The model will include baseline CDR-SB as a covariate, with treatment group and randomization stratification variables as factors.

Analysis for Chinese Subjects

LS mean and 95% CI for the difference between treatment groups as well as LS means and SE for each treatment group will be estimated using MMRM similar to the primary analysis. The treatment effect in Chinese subjects will be examined against the overall population using a forest plot.

5.4.2 Secondary Efficacy Analyses

The secondary endpoints 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 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

Time to worsening of CDR scores by 24 months

Time to worsening of CDR scores by 24 months will be analyzed on the FAS using a 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 - increase from baseline by at least 0.5 points on the global CDR score, 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 by 24 months for subjects who were not clinically staged as dementia at Baseline based on clinical diagnosis

This endpoint will be analyzed on the FAS using a 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 in clinical diagnosis. Time to conversion to dementia for subjects who were not clinically staged as dementia at baseline is defined as time from randomization to conversion to dementia in clinical diagnosis. For subjects without clinical dementia by the end of study, the time to conversion to dementia will be censored at the date of last dementia diagnosis.

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 rate of change over time (mean slope) based on CDR-SB score over 24 months

The rate of change over time (mean slope) for the change from baseline in 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.

Other continuous endpoints

The other continuous secondary efficacy endpoints will be analyzed using the same MMRM model as the primary efficacy analysis to compare elenbecestat (E2609) 50 mg versus placebo on the FAS, using baseline value corresponding to the response variable in the model. These endpoints include:

- 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

With regard to the change from baseline in ADAS-cog$_{14}$ Word List, it includes the immediate and delayed recall tasks, their scores will be part of the ADAS-cog$_{14}$ assessment (Item 1 and 4).

5.4.3 Biomarker Endpoints

The biomarker endpoints are changes from baseline in:

- Amyloid PET SUVR composite at 24 months for brain amyloid levels
- CSF biomarkers t-tau and p-tau at 24 months
- CSF amyloid biomarkers Aβ(1-40), Aβ(1-42), and Aβ(1-x) at 24 months
- Total hippocampal volume at 24 months using vMRI
- Preservation of connectivity on fMRI at 24 months

The analysis of the above endpoints will be performed by using MMRM or ANCOVA model, 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.

The relationship between clinical changes (CDR-SB, ADAS-cog$_{14}$, MMSE, and FAQ) and changes in 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 of clinical scale as a covariate, randomization stratification variables and treatment group as factors, and other terms as appropriate.

The relationship between exposure (in CSF, plasma) of elenbecestat (E2609) with potential biomarkers of Alzheimer's disease as deemed appropriate will be evaluated using ANCOVA model with changes in biomarker at 24 months as response variables and exposure variables (in CSF, plasma) of elenbecestat (E2609) as independent variables.

5.4.4 Exploratory Endpoints

The exploratory endpoints 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

Time to change of concomitant AD treatment will be analyzed similarly as that used for the time to conversion to dementia based on clinical diagnosis, as described in the 2nd endpoints. 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 as that used for the proportion of subjects with dementia diagnosis at 24 months, as described in section 6.4.2.

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 as that used for the rate of change over time (mean slope) for the change from baseline in CDR-SB, as described in section 6.4.2.

Analysis of the change from baseline exploratory endpoints will be performed to compare elenbecestat (E2609) versus placebo by using MMRM or ANCOVA model. For each of them, the treatment effect of elenbecestat (E2609) 50 mg per day versus placebo will be tested at a significance level of 2-sided alpha = 0.05. These endpoints include:

- 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

5.5 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.

5.5.1 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.

5.5.2 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, concurrent treatment with AChEIs or memantine (no, yes), and clinical dementia (no, yes).

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.

5.5.3 Laboratory Values

Laboratory results will be summarized using International System of Units, as appropriate. For all quantitative parameters, 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 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.

Section 12.1 (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.

5.5.4 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.

In addition, frequency counts of clinically notable vital signs will be summarized by treatment group. Table 3 presents the clinical notable ranges.

Table 1. Clinical Notable Ranges for Vital Signs

Vital Sign	Criterion for Low	Criterion for High
Pulse (bpm)	< 50	> 100
Temperature (°C)	< 36	> 38
Weight (kg)	< 45	> 100
Systolic BP	< 90	> 160
Diastolic BP	< 50	> 100

5.5.5 Electrocardiograms

Descriptive statistics for ECG parameters and changes from baseline will be presented by visit and treatment group. Shift tables will present changes from baseline in ECG interpretation (categorized as normal; abnormal, not clinically significant; and abnormal, clinically significant) to the end of treatment.

In addition, the number (percentage) of subjects with at least 1 post-baseline abnormal ECG result in QTcF during the treatment period will be summarized. Clinically abnormal ECG results in QTcF will be categorized as follows:

Absolute QTc interval prolongation:

- QTc interval >450 msec
- QTc interval >480 msec
- QTc interval >500 msec

Change from baseline in QTc interval:

- QTc interval increases from baseline >30 msec

- QTc interval increases from baseline >60 msec

5.5.6 C-SSRS

The C-SSRS responses will be mapped to C-CASA. The incidence of new or worsening suicidal ideation or suicidal behavior will be summarized by treatment group. Continuous variables will be summarized by descriptive statistics; number of subjects, mean, standard deviation, median, minimum, and maximum and categorical variables by number (percentage) of subjects.

5.5.7 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.

vMRI will be used to evaluate disease modification as indicated by measurements of brain atrophy. 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.

5.6 Pharmacokinetic, Pharmacodynamic, and PHARMACOGENOMIC/PHARMACOGENETIC ANALYSES

Pharmacokinetic Analyses

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.

Pharmacokinetic - Pharmacodynamic Analyses

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 scores (CDR-SB, CDR global score, and CDR Memory Box score) at 24 months (including both absolute score and the change from baseline), 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.

Details of further analyses of pharmacokinetic/pharmacodynamic data will be described in a separate PK/PD analysis plan.

5.7 OTHER ANALYSES

No other analyses are planned.

6 INTERIM ANALYSIS

There is no interim analysis of efficacy, but there will be a futility analysis 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.

7 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

7.1 DEFINITION OF BASELINE

The baseline value for efficacy, biomarker and safety will be defined as data collected prior to and/or on the date of first dose, usually the same day as the Day 1 (Visit 2). If there is more than one value on or before Day 1, the value closest to and prior to (including on) the date of first dose will be used as the baseline value.

7.2 ALGORITHMS FOR EFFICACY PARAMETERS

This section describes the algorithms and missing data handling procedure to derive the totals scores for the efficacy parameters: CDR, ADAS-Cog_{14}., MMSE, and FAQ.

CDR: The CDR is a clinical global rating scale requiring the interviewing of both the subject and an informant 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 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.

ADAS-cog_{14}: The ADAS-cog is the most widely used cognitive scale in AD clinical studies. The 14-item version (as shown in Table 4) is considered more sensitive for less impaired populations such as MCI/Prodromal and mild AD subjects.

Table 2. ADAS-cog_{14} Items and Algorithm for Derivation of Item Scores and Total Score

Item	Algorithm	Handling Missing Data	Score Range
1. Word Recall	Total the number of "No" responses for each trial. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 10
2. Commands	Total the number of "No" responses from the 5 tasks	If any task is missing then the subscore is missing	0 to 5
3. Constructional Praxis	Count the number of "No" responses. The subscore is	If any task is missing then the subscore is missing	0 to 5

	0 = all 4 drawings correct 1= 1 figure drawn incorrectly 2= 2 figures drawn incorrectly 3= 3 figures drawn incorrectly 4= 4 figures drawn incorrectly 5= no figures drawn, scribbles, parts of forms		
4. Delayed Word-Recall	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 10
5. Naming Objects / Fingers	Total the number of "No" responses. The subscore is 0= 0-2 "no" responses 1= 3-5 "no" responses 2= 6-8 "no" responses 3= 9-11 "no" responses 4= 12-14 "no" responses 5= 15-17 "no" responses	If any response is missing then subscore is missing	0 to 5
6. Ideational Praxis	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 5
7. Orientation	Total the number of "No" responses.	If any response is missing then subscore is missing	0 to 8
8. Word Recognition	For each trial, total the number of "1" responses. If the total is 12 or less, then the trial score = total. If the total is > 12 then trial score=12. The subscore is the sum the scores from trials 1, 2, and 3, divide by 3.	If a trial is missing or partially done then trial score is missing. If a trial score is missing then the subscore is missing	0 to 12
9. Remembering Test Instructions	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
10. Comprehension	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
11. Word Finding Difficulty	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
12. Spoken Language Ability	The subscore is 0= None, 1= Very Mild, 2= Mild, 3= Moderate, 4= Moderately Severe, 5= Severe	If the response is missing then subscore is missing	0 to 5
13. Executive Function (Maze)	The subscore is based on the total number of seconds to complete the task and/or whenever the task was stopped due to 2 errors being made, as follows; 0 = 0-30 seconds 1 = 31-60 seconds 2 = 61 – 90 seconds 3 = 91 – 120 seconds 4 = 121-239 seconds	If the response is missing then the subscore is missing	0 to 5

	5 = 240 seconds or at least 2 errors		
14. Number Cancellation	Adjusted Score = Total # correct targets crossed off minus Total # incorrect targets crossed off minus Total # times reminded of task. Then use Adjusted Score to determine the subscore as follows; Adjusted Score = Subscore ≥23 = 0 18-22 = 1 13-17 = 2 9-12 = 3 5-8 = 4 ≤4 = 5	If any component of the adjusted score is missing then the subscore is missing	0 to 5
Total Score	Total Score = sum of the subscores above	If any subscore is missing then Total Score is missing	0 to 90

MMSE: 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. MMSE is composed of 30 questions group into domains. For each of the MMSE domains add the correct responses. If a domain has missing data then the domain is missing. From the domains, one can compute the six items as show in Table 5. If any domain is missing then the item is missing. The MMSE Total Score (range 0 to 30) = sum of the six items. If any item score is missing then the Total Score is missing.

Table 3. MMSE Domains and Items

Domain	Score Range	Item	Score Range
1. Orientation to Time	0 to 5	1. Orientation to Time	0 to 5
2. Orientation to Place	0 to 5	2. Orientation to Place	0 to 5
3. Registration	0 to 3	3. Registration	0 to 3
4. Attention and Calculation[a]	0 to 5	4. Attention and Calculation	0 to 5
5. Recall	0 to 3	5. Recall	0 to 3
6. Naming	0 to 2	6. Language (Sum of Naming, Repetition, Comprehension, Reading, Writing, and Drawing)	0 to 9
7. Repetition	0 to 1		
8. Comprehension	0 to 3		
9. Reading	0 to 1		
10. Writing	0 to 1		
11. Drawing	0 to 1		
		Total Score	**0 to 30**

[a] Spell WORD Forward, then Backward score is only use if Attention and Calculation score is not available

FAQ: The FAQ is composed of 10 activities. Each activity is rated as 0 = Normal, 1 = Has difficulty but does by self, 2 = Requires assistance, 3 = Dependent, 8 = Not Applicable. The Total Score is the sum of the 10 activity. If any activity is missing then the Total Score is missing. Activities marked as "Not Applicable", are not use in the computation of the Total Score. However, in order to account for "Not Applicable" activity(s), the Total Score is weighted as follows;

Total Score = Total Score x 30 / (30 minus 3 times the number of activities marked "Not Applicable")

8 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

9 STATISTICAL SOFTWARE

All statistical analyses will be performed by Eisai Inc., using SAS Version 9.3.

10 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

11 REFERENCES

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12 APPENDICES

12.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table 7 of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 1.

Table 4. 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

	Grade 1	Grade 2	Grade 3	Grade 4
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 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).

ELECTRONIC SIGNATURES

Signed by	Meaning of Signature	Server Date (dd-MMM-yyyy HH:mm 'GMT'Z)
PPD	Biostatistics Approval	29-Mar-2017 16:59 GMT-04
	Document Originator Approval	29-Mar-2017 17:01 GMT-04
	Biostatistics Approval	29-Mar-2017 17:54 GMT-04
	Medical Monitor Approval	30-Mar-2017 04:19 GMT-04

Data Safety Monitoring Board

Elenbecestat (E2609) Program Charter

Investigational Product	**Elenbecestat is the proposed International Nonproprietary Name (pINN) for E2609**
Study Protocol Number:	**E2609-G000-202**
Study Title:	**A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to the Evaluate Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease**
Study Protocol Number:	**E2609-G000-301**
Study 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**
Study Protocol Number:	**E2609-G000-302**
Study 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**
Date of Document	**27 February 2017**
Version	**Final 1.0**

Reviewed and Accepted at Eisai by:

PPD

14 April 2017
Date

Table of Contents

1. INTRODUCTION

This Charter is for the Data Safety Monitoring Board (DSMB) for the elenbecestat (E2609) Program to include protocols E2609-G000-202: A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease being conducted in the U.S.; E2609-G000-301: 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 that is being conducted globally; and E2609-G000-302: 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 that is being conducted globally. Overviews of each study may be found in Appendix 1, Appendix 2, and Appendix 3 respectively. The Charter defines the primary responsibilities of the DSMB, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The Charter also provides the procedures for ensuring confidentiality in alignment with the Agreement, proper communication, the procedures for preparation of Closed Reports (confidential information on the analysis of unblinded safety data) and an outline of the content of the Closed Reports that will be provided to the DSMB. Eisai, Inc. is the Sponsor of the study; DSMB Coordination support is provided by the Pharmaceutical Product Development (PPD) DSMB Coordination Staff (DCS).

2. PRIMARY RESPONSIBILITIES OF THE DSMB

- The DSMB is primarily responsible for protecting the safety of trial participants.
- The DSMB will conduct an unblinded review of the safety data during the trials and advise Eisai on issues pertaining to safety.
- Review and approve the DSMB Charter by signing a Charter Approval page (Appendix 4) documenting their approval of the Charter.
- Review and approve the Organizational Meeting Minutes as well as the open and closed session minutes of each DSMB meeting.
- Maintain confidentiality of all trial related information as described in the legal Agreement between the parties. Members will be asked to sign a document destruction statement at the beginning of the study in the event documents are downloaded from the website or provided via password protected email. At the end of the trial or individual involvement, members will be asked to sign a confirmatory statement indicating any and all confidential documents remaining in their possession have been destroyed (Appendix 5).

3. PRIMARY RESPONSIBILITIES OF EISAI

- Drafts and finalizes the contractual agreements between Eisai and the DSMB members.
- Provides support for DSMB requests for production of SAS programs.

- Provide approval for submission of redacted charter to regulatory authorities as needed.
- Serve as the primary contact with the Institutional Review Boards (IRB) and Independent Ethics Committees (IEC) for DSMB inquiries.
- Send blinded safety data to the Independent Unblinded Biostatistician.
- Arrange for the Independent Unblinded Biostatistician to have access to the Interactive Web Response System (IWRS) to obtain the unblinded treatment codes.
- Update the DSMB during the open sessions of DSMB meetings on the status of the studies.
- Inform the DSMB of any amendments to the study protocols, changes to the conduct of the studies, updates or amendments to the Investigator Brochure (IB), and safety information regarding Study E2609-G000-202, Study E2609-G000-301, or Study E2609-G000-302, via the DCS.
- Designate members of Eisai's senior management team who will review the DSMB recommendations and decide on their implementation.
- Appoint PPD to provide support to the DSMB or to assign another group this role in the future at which time the Charter would be amended.

4. RESPONSIBILITIES OF THE PPD DSMB COORDINATION STAFF (DCS)

The DCS consists of a DSMB Coordinator/Principal Safety Specialist and a Safety Administrator IV who are not involved in the day-to-day management of the studies. Responsibilities include:

- Assist Eisai and the DSMB with development of the Charter and subsequent revisions as needed.
- Coordinate DSMB meetings and meeting logistics as needed.
- Set up and maintain the electronic DSMB Master Files and the secure DSMB website.
- Generate draft open and closed session minutes, distribute for review as appropriate (closed session minutes to the DSMB/Independent Unblinded Biostatistician only, open session minutes to the DSMB/Eisai).
- Finalize, circulate for signature, and post final minutes and recommendation forms to the respective secure websites. Scanned signatures received via email or faxed signatures are acceptable; wet-ink signatures on minutes and charters are not required.
- Ensure the security of the Eisai DSMB website via user-defined access control.
- Archive data deliverables for each of the safety review meetings on the secure DSMB website.
- Compile and maintain the following documents in the DSMB Master File. The documents will be stored in a secured electronic area with access limited to the DCS and forwarded to Eisai for archiving upon completion of the study:
    - All versions of the charter and associated attachments;
    - All versions of the IB, protocol and associated amendments;

- Copies of *ad hoc* reports and any other reports provided to the DSMB (as applicable);
- Minutes (open and closed sessions) and completed Chair Recommendation Forms from each DSMB meeting;
- Copies of all meeting materials provided to the meeting attendees;
- Documentation of destruction of meeting materials from each member;
- Copies of significant and relevant correspondence related to this DSMB;
- Serious Adverse Event (SAE) reports

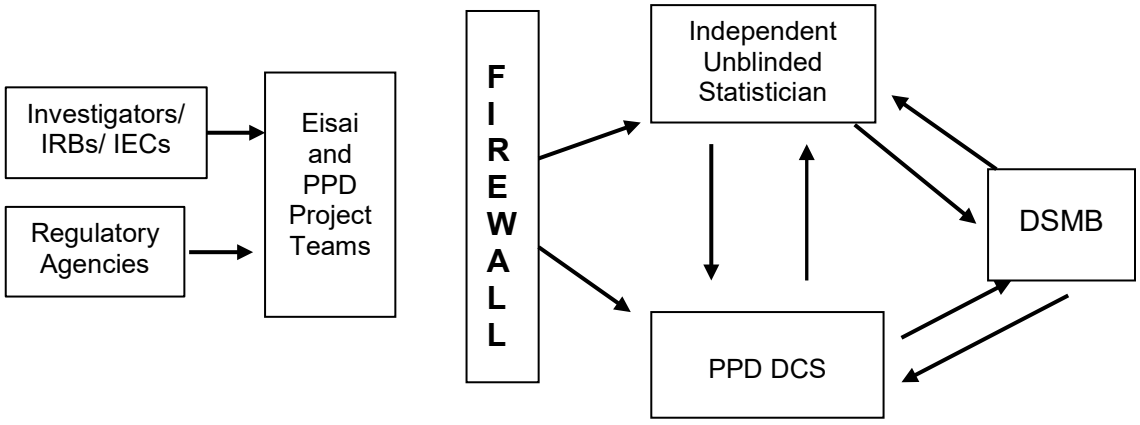
5. RESPONSIBILITIES OF THE INDEPENDENT UNBLINDED BIOSTATISTICIAN

The Independent Unblinded Biostatistician is a non-voting consultant to the DSMB, designated by Eisai from an external organization, not involved in daily activities of studies E2609-G000-202, E2609-G000-301, or E2609-G000-302 and has no responsibilities other than those involved in preparing and providing information for the DSMB.

Responsibilities include:

- Accessing the IWRS to obtain the treatment codes and generating the unblinded output for each study for the DSMB.
- Generating the unblinded tables, listings, figures (TLFs) for each study for DSMB review prior to safety review meetings.
- Attending the closed session of DSMB meetings for support during TLF discussion.

The following diagram shows the relationships between the DSMB and others involved in the trial:



6. MEMBERSHIP OF THE E2609 PROGRAM DSMB

6.1 Members

The E2609 Program DSMB is an independent multidisciplinary group, consisting of a biostatistician and clinicians, who collectively, has experience in the management of patients with

Alzheimer's disease (AD), general internal medicine, cardiology, neurology, psychogeriatrics, neuropsychology and clinical immunology as well as experience in the conduct and monitoring of randomized blinded clinical trials. Membership of the DSMB is restricted to individuals who are not debarred or disqualified by FDA or other regulatory authorities; the DCS will consult the debarment list as needed. Evidence of qualifications including current curriculum vitae (CV) should be provided to Eisai prior to establishment of the DSMB.

The DSMB will include up to four (4) clinicians, one (1) of whom will be the DSMB Chair, and a statistician; all five (5) are voting members.
Requirements for these members are as follows:

- Experienced in the evaluation of a treatment intervention compared to placebo.
- Accreditation in their fields including but not limited to neurology, psychology, psychiatry, geriatrics, general internal medicine, cardiology, clinical immunology, or neuropsychology.
- Prior clinical and/or research experience with AD or geriatric populations.
- Prior involvement in other randomized blinded clinical trials is required. It is desirable but not required that members have served on DSMBs for other studies involving AD evaluating a treatment intervention compared to placebo.
- The Statistician is required to have experience on other DSMBs in clinical trials.

6.2 Conflicts of Interest

DSMB members should not have direct involvement in the conduct of the studies and will be required to sign a Conflict of Interest (COI) statement. The DSMB membership is restricted to individuals free of unmanageable conflicts of interest. The source of these conflicts may be financial, proprietary, professional scientific, regulatory, or other interests that may affect impartial, independent decision-making by the DSMB. Thus, neither study investigators nor individuals employed by either Eisai or its collaboration partner Biogen, Inc. or members of their families, nor individuals with regulatory responsibilities for the trial products, are eligible for membership of the DSMB. The DSMB members will disclose to Eisai and to fellow members any consulting agreements or financial interests they have with any Eisai company, the collaboration partner Biogen, Inc., any third party vendors, or with any of the Contract Research Organizations (CRO) involved in the program. Eisai and the other DSMB members will be responsible for deciding whether these or any other consulting agreements or financial interests materially impact their objectivity, or appear to pose a significant conflict of interest.

In order to avoid bias, members should not have a financial or research collaboration involving any elenbecestat (E2609) study with a participating investigator.

Relevant conflicts of interest may include:

- A financial interest that could be substantially affected by the outcome of the clinical trials; such an interest might include a monetary stake (e.g., stock options or ownership interests) in Eisai, Biogen Inc., PPD, inVentiv Health, third party vendor, or a competing company.
- A proprietary interest (e.g., patent, trademark, copyright, licensing agreement, etc.) in the product tested in the clinical trials.
- A monetary interest in an ancillary device or product that would change in commercial value based on the outcome of the clinical trials.
- A professional or career prospect that would be altered by the outcome of the clinical trials.
- Active involvement in study design, conduct, or daily management of the elenbecestat (E2609) clinical trials.
- Personal or professional relationships with those in trial leadership positions, at Eisai or at investigational sites that could be considered reasonably likely to affect objectivity.
- Concurrent service as a member on other DSMBs for related or competing products.
- Strong positive or negative views on the relative merits of the intervention under study that might preclude review of data in a fully objective manner.
- Other interests that may affect impartial, independent decision-making.

At the beginning of each meeting, the DCS will ask the members to disclose any changes in the status of their conflict of interest; all responses will be documented in the meeting minutes. Prior to any discussion, the DSMB members will be responsible for advising fellow members and Eisai of any additional relationships that may be construed as conflicts of interest that are established during the course of the trial. A DSMB member, who, during the course of the trial, enters into a relationship that, in the judgment of Eisai and the DSMB members, constitutes significant conflict(s) of interest, as defined above or otherwise, must resign from the DSMB.

The term of membership is for the duration of the protocols included in the program. If a member leaves the DSMB during the course of the program, or does not fulfill his/her obligations, Eisai will select a replacement in a timely manner that fulfills all the previously stated requirements. The DSMB or Eisai may request a change (i.e., replacement or an addition) to DSMB membership. In the event a member/Chair resigns, or the decision is made by the DSMB, Chair and/or Eisai to remove a member/Chair, a replacement will be appointed in a timely manner. Should the Chair resign or be replaced, an interim Chair will be appointed until a replacement is selected. A DSMB member may be replaced for any of the following reasons:

- The DSMB member elects not to continue participation.

- The DSMB member becomes incapable of fulfilling DSMB responsibilities or adhering to the DSMB charter.
- The DSMB member develops a conflict of interest.
- The DSMB member is disqualified, restricted, or debarred by a health authority or regulatory agency.
- The DSMB member breaches any of his/her contractual obligations.

Any proposed change in membership will be discussed within the DSMB, who will make a recommendation regarding the change of membership to the Eisai study director or study team. In consultation with the DSMB, Eisai will make final decisions regarding replacement or addition of DSMB members.

In addition to the payment of consulting fees to each member of the DSMB, Eisai will reimburse other reasonable travel and expenses related to the DSMB meetings. The DCS will assist Eisai as needed with meeting logistics.

DSMB members must be willing to allow Eisai to share information relating to the membership and any potential conflicts of interest with regulatory authorities, if such information is requested; otherwise, the identities/contact information of the members will be kept confidential.

7. TIMING AND PURPOSE OF THE DSMB MEETINGS

7.1 Organizational Meeting

The Organizational Meeting was conducted 23 January 2015, prior to the first subject randomized in the E2609-G000-202 study. The purposes of the meeting was to define the roles and responsibilities of DSMB members, to discuss and approve the DSMB Charter, discuss and approve the format of the safety TLF shells, and the format and content of the Open and Closed Reports that will be used to present trial results at future meetings. The Organizational Meeting was attended by the DSMB members, the Independent Unblinded Biostatistician, the DCS, and the Medical Monitor from the CRO for the study, and representatives from Eisai and/or the CRO's Clinical Operations group. The DSMB was provided with the E2609-G000-202 clinical trial protocol, IB, draft DSMB Charter, and the draft TLF for review. An abbreviated Organizational Meeting will be conducted when a new protocol is added to the E2609 Program. This abbreviated meeting may be combined with the open session of a data review meeting; the new study protocol will be provided for review prior to the meeting. The charter will also be revised as protocols are added and will be provided to the DSMB for review and approval.

7.2 Safety Review Meetings

During the safety review meetings, the DSMB will discuss cumulative safety data. The following schedule of safety review meetings will be adhered to by the DSMB.

7.2.1 Scheduled Safety Review Meetings

The DSMB will meet formally to review safety data at defined time points as described in the protocol-specific appendix (Appendices 1, 2, and 3); the review meetings may be held in person or via teleconference; the format will be at the discretion of the DSMB and Eisai.

The DSMB will make recommendations to Eisai based on the safety review. Following each meeting, the Chair will complete and sign a DSMB Chair Recommendation Form for each study (Appendix 6) and provide it to the DCS for distribution to the designated Eisai representative.

7.3 *Ad hoc* Meetings/Reports

Ad hoc meetings may be requested by Eisai or by the DSMB, if either party believes it is warranted for issues related to patient safety, or for the purpose of conveying new information relevant to the activities of the DSMB.

The DSMB may, at any time, request additional safety data and safety analyses in an agreed upon format. Subject to approval by Eisai, additional safety analyses apart from those specified in the DSMB TLF, may also be included if DSMB thinks such analyses are valuable in assessing the safety profile. Therefore, additional Closed Reports on such additional safety analyses may be created.

8. CONFIDENTIALITY AND COMMUNICATION PROCESSES

Members of the DSMB must sign a contractual agreement (DSMB Agreement) containing detailed confidentiality terms and obligations prior to receiving any confidential or proprietary information or providing services for the DSMB, and must agree to hold in confidence all study-related data/analyses/documents, verbal or written communications.

To maintain the integrity and credibility of the trials, processes will be implemented to ensure the Independent Unblinded Biostatistician and supporting independent programmer, if applicable, have exclusive access to unblinded datasets; the DCS will receive the unblinded TLF for distribution to the DSMB. DSMB members should take care to maintain the blind of Eisai study team and agents of Eisai (e.g., employees of Eisai, Biogen, Inc., PPD, inVentiv Health) at all times for the duration of the trials, unless otherwise specified in this DSMB Charter, until after the study database is locked and the treatment groups for the entire study are unblinded.

Processes will be implemented to ensure proper communication is achieved between the DSMB and Eisai. The DCS will be the liaison for communication/information to and from the DSMB. No communication, either written or oral, of the content of the studies, conduct of the studies, DSMB deliberations or DSMB recommendations will be made outside of the DSMB except as provided for in this Charter; administrative communication is acceptable. The DSMB will conduct its deliberations in private and maintain strict confidentiality of all data, minutes, and discussions beyond the recommendations communicated to Eisai at the conclusion of the safety review meetings. To provide a forum for exchange of information among various parties who share responsibility for the successful conduct of the trials, a format of open sessions and closed sessions will be implemented for DSMB meetings. The intent of this format is to enable the DSMB to preserve confidentiality while providing opportunities for interaction between the DSMB and blinded study team members who may have valuable insights into trial-related procedures.

Neither the DSMB nor any of its members shall make any public announcements relating to the recommendations, proceedings, actions or activities of the DSMB or Eisai in connection with the studies, except as may be permitted under the Agreement or unless such DSMB member is required to disclose such information pursuant to court or governmental action and provided that Eisai is notified promptly of any such disclosure requirement and, after all reasonable remedies for maintaining such information in confidence have been examined. Eisai is afforded the opportunity, to the extent practicable, to dictate the manner and timing of any such disclosure.

To protect the confidentiality and security of the unblinded safety TLF, information/material for DSMB review will be posted to a secure, access controlled website. The DCS will be responsible for initiating set up of the site and requesting access for the DSMB members and Eisai. Two separate sections will be created on the website; the ‘DSMB Members’ section accessible by the DSMB, the Independent Unblinded Biostatistician and the DCS only, and the ‘General Information’ section accessible by Eisai and other blinded team members as approved by Eisai. A user-name and password are provided to each individual for access to view the appropriate section of the website. As a component of maintaining confidentiality, unblinded safety information should not be shared with anyone other than DSMB members and those support personnel attending the closed sessions of the meetings. Any confidential or unblinded information shared among the DSMB members by email must be password protected prior to transmission.

The DCS will be responsible for maintaining the website, granting or denying access, and have exclusive posting rights to both areas. The ‘DSMB Members only’ section will be used to post/archive all meeting materials and reports provided to the DSMB including the Closed Reports, open and closed minutes, recommendation forms, current versions of the protocol, IB, and the current final DSMB Charter. The ‘General Information’ section will contain open session

minutes, recommendation forms, meeting agendas, current versions of the protocol, IB, and the current final DSMB charter.

9. DATA FOR REVIEW

9.1 Data for Safety review meetings - Closed Report

The clinical electronic data capture (EDC) database will be used by Eisai data analysis group for preparation of the blinded datasets for each study. All safety analyses will be based on the clinical database. The Independent Unblinded Biostatistician will download the blinded datasets, located on the sFTP server, before each DSMB review meeting. The unblinded randomization data will be accessed by the Independent Unblinded Biostatistician directly from the IWRS database in order to generate the DSMB Closed Report by protocol for each DSMB safety review meeting, *ad hoc* meeting, or *ad hoc* unblinded analyses requested by the DSMB.

The DSMB closed reports will be prepared by the Independent Unblinded Biostatistician, per the agreed TLF, and provided to the DCS for distribution to the DSMB via the secure website at least five (5) business days prior to the meeting date. The DCS will notify the DSMB via email that the reports have been posted and are available for review.

Details of the unblinded analysis of safety data and format of the results will be described in the study Statistical Analysis Plan (SAP).

Eisai Product Safety will also provide the following reports, by individual protocol, to the DCS for distribution to the DSMB at least 1 week prior to each DSMB safety review meeting:

- A blinded line listing in Excel format of all SAEs
- Council for International Organizations of Medical Sciences (CIOMS) reports of SAEs (which may be blinded or unblinded) to the DSMB under Section 9.2 (below).
- These reports may include data from subjects randomized to placebo or E2609.

9.2 Data for Ongoing Review

For each protocol, Eisai Product Safety will provide the DCS with information on SAEs for distribution to the DSMB. CIOMS reports for SAEs which are unexpected and suspected to be related to E2609, will be provided to the DCS within fifteen (15) days of the receipt of the event by Eisai Safety, for distribution to the DSMB via the secure website. The DCS will notify the DSMB via email when the information is posted and available for review.

10. MEETING FORMAT

Meetings will consist of at least two (2) sessions: Open and Closed, with optional Debriefing Session and Executive Sessions.

10.1 Quorum Requirement – DSMB Decision Making

Attendance of four (4) out of five (5) members will be required to fulfill the quorum requirement; the Chair and Biostatistician are required to attend in order for a meeting to be conducted. The opinion of the absentee member will be solicited by the Chair and shared with the DSMB. All efforts will be made to achieve a unanimous agreement. If the DSMB is unable to reach unanimity, a consensus will suffice; and a consensus will be required on a recommendation to modify or terminate the trial. Any dissenting opinions will be recorded in the closed session minutes. If, at the time of a meeting, a member has resigned and a replacement has not yet been named, and there is a tie vote, the DSMB Chair casts the deciding vote.

10.2 Open Session - Blinded

The open session includes clinical/translational medicine, safety/pharmacovigilance (PVG) and biostatistical representatives from Eisai, the CRO Medical Monitor, the DSMB members, the Independent Unblinded Biostatistician and the DCS. During this session, only blinded data will be discussed. The objective of the open session will be to update the DSMB on the conduct of all studies including site status, enrollment rates, screen failures, timelines of data submissions and other administrative data. Eisai may pose specific verbal or written questions to the DSMB for consideration during the closed session. The clinically-appropriate DSMB member may be called upon to provide expert advice to Eisai regarding matters such as safety concerns or diagnostic evaluations in individual subjects in the open session. The DCS will reconfirm the status of each DSMB member's conflict of interest statements at the beginning of the open session.

10.3 Closed Session - Unblinded

The closed session includes the DSMB members, the Independent Unblinded Biostatistician, and the DCS. In order to ensure that the DSMB is fully capable of performing its primary mission of safeguarding the interest of participating subjects, the DSMB will be unblinded in its assessment of safety data. During the closed session unblinded data summaries for each study will be presented by the Independent Unblinded Biostatistician, discussed by the DSMB, and recommendations formulated and voted on by the DSMB. If the members have specific questions regarding the conduct or data for any study, they may return to an open session format and the appropriate Eisai representatives will be contacted to respond. During any such intervening open sessions, unblinded data will not be discussed with Eisai personnel. At the conclusion of the closed session, the DSMB is expected to reach a conclusion about study conduct and safety.

10.4 Debriefing Session – DSMB Recommendations

In the event of significant DSMB recommendations, a debriefing session may be conducted either immediately following the closed session or in the weeks following the meeting if additional analysis or data are required prior to making the recommendations. If conducted, this session includes DSMB members, the DCS, and the designated Eisai representative. During this session,

the Chair will provide a verbal report of the DSMB recommendations for each study and address any outstanding questions from Eisai in a blinded manner. All recommendations and discussions will be recorded in the minutes. The Chair will complete a Chair Recommendation Form for each study and provide the forms to the DCS for submission to the Eisai representative within 48 hours following the meeting. The DCS will generate a redacted (Chair name/signature) version of the forms and provide to Eisai in the event it is needed for further distribution. The completed recommendation forms should not contain confidential information and should be completed in a blinded manner, such that, if warranted, the redacted version can be circulated by Eisai to investigators, IRB/IEC, regulatory authorities, and/or other interested parties.

10.5 Executive Session

If requested by the DSMB, an Executive Session may be conducted following the closed session for discussion outside the presence of the DCS and the Independent Unblinded Biostatistician. Attendees will be limited to the DSMB only. The Chair will be responsible for generating, circulating to the DSMB for review, and archiving of the Executive Session minutes. Following the Executive Session, the Chair will contact the DCS and provide instructions for next steps (debriefing session or conclusion of meeting).

10.6 Post-Meeting Activities

At the completion of a face to face DSMB meeting, the DCS will collect copies of all unblinded TLF/study documents and ensure that these are secured and ultimately destroyed to minimize the potential for a breach of confidentiality. Following teleconferences, documents are destroyed as noted in the document destruction statement.

10.7 Eisai Decisions

The DSMB is an advisory board only; final decisions regarding the future of the studies are the responsibility of Eisai. Decisions on study termination, amendment, or cessation of subject recruitment, based on safety or outcome findings, will be made by Eisai after recommendations from the DSMB have been assessed. Decisions regarding the appropriate potential steps will be made by Eisai in consultation with the DSMB, and/or relevant regulatory authorities, as required. Eisai will document acknowledgement of receipt and response to the recommendations on the Chair Recommendation Forms and return them to the DCS; the completed forms will be posted to both sections of the secure website. DSMB concurrence will be sought on all substantive changes resulting from its recommendations.

If the DSMB recommends a significant alteration of the trials or stopping any of the trials, Eisai representative(s) may request an open meeting with the DSMB to review the recommendations. If the DSMB recommends that the clinical trials be terminated, but Eisai decides to continue the trials, Eisai will provide the DSMB with a written explanation of that decision within two (2) weeks.

Eisai is responsible for reporting any DSMB recommendations to stop a study, and Eisai's response to the recommendation, to all appropriate regulatory agencies in a timely manner.

11. DSMB MEETING MINUTES

For each study, the DCS will prepare draft minutes of the open and closed sessions for review and subsequent approval within two (2) weeks of each meeting. Minutes should be brief and focused; however, all opinions must be recorded. The draft open minutes will summarize the discussion in the open session and include the verbal recommendations as provided by the Chair. Eisai will return comments, suggestions, or proposed revisions to the minutes to the DCS. Comments will be incorporated and the DCS will forward the revised draft open session minutes to the DSMB for review. Comments will be incorporated and the minutes will be finalized and circulated for signature. The open minutes will be signed by the DSMB Chair and Eisai.

The closed minutes will summarize the discussion during the closed session, voting on recommendations, and the final recommendations to be presented to Eisai. Review and discussion of updates to or additional unblinded TLF arising from the closed session will be documented in the closed minutes as post-meeting information. The closed session minutes will be forwarded to the Independent Unblinded Biostatistician for review; comments incorporated, then forwarded to the DSMB for review. Comments will be incorporated; the minutes will be finalized and circulated for signature. The closed minutes will be signed by the DSMB Chair and the final minutes posted to the 'DSMB Member only' section of the website. The final open session minutes will be posted to the 'DSMB Members only' and the 'General Information' sections of the secure website.

12. DOCUMENT RETENTION

The DCS will compile and maintain the following documents for each study in the electronic DSMB Master File. The documents will be stored in a secured electronic area with access limited to the DCS and forwarded to Eisai for archiving upon completion of the study:

- All versions of the charter and associated attachments;
- All versions of the IB, protocol / protocol amendments;
- Copies of the reports provided to the DSMB (as applicable);
- Minutes (open and closed sessions) and completed Chair Recommendation Forms from each DSMB meeting;
- Copies of all meeting materials provided to the meeting attendees;
- Signed document destruction statements (start and end of program);
- Copies of significant and relevant correspondence related to this DSMB.

APPENDIX 1: E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's disease Amendment 7, dated 01 February 2017

This is a Phase 2, multicenter, placebo-controlled, double-blind, parallel-group, randomized, dose-finding study in subjects with mild cognitive impairment (MCI)/Prodromal Alzheimer's Disease (AD) or mild to moderate AD. Following completion of the Pre-randomization Phase (up to 60 days plus an additional 30 days if required), and eligibility confirmed by all screening assessments, approximately 60 eligible subjects (MCI/Prodromal and mild to moderate AD) will be randomized 1:1:1:1 to four (4) treatment groups (5, 15, or 50 mg E2609 or placebo) within each of the study populations.

The primary objective is to assess the safety (including immunological and hematological parameters) and tolerability of daily dosing with E2609 in MCI/Prodromal subjects and in subjects with Mild to Moderate Dementia due to Alzheimer's Disease. Secondary objectives include to characterize the pharmacokinetic (PK) effects of E2609 in plasma and cerebrospinal fluid (CSF), and to assess the effects of E2609 on amyloid β (1-x) [Aβ (1-x)] and Aβ (1-42) in CSF from four (4) weeks and up to 18 months of treatment.

The DSMB will conduct unblinded safety reviews approximately every three (3) months, from the date the first subject was randomized until the last subject is randomized in the study. In order to make decisions about the remainder of the study as well as the full E2609 clinical development program, the sponsor will unblind safety, PK, and pharmacodynamic (PD) data on an ongoing basis and perform interim analyses of these data. Investigators, other clinical site staff, subjects, caregivers/informants and study team will remain blinded to study treatment.

Once subjects have completed at least 12 weeks of treatment (or discontinued study drug early) an interim safety analysis will be conducted by Eisai and the DSMB. Subjects will continue study drug during the safety review by the DSMB. The DSMB will provide recommendations to Eisai after each review as to whether any change(s) to the study are necessary. After the completion of the interim safety analysis, all unblinded safety reviews conducted by the DSMB will coincide with that of the Phase 3 E2609 studies.

Safety analysis parameters include the incidence of AEs (including changes from baseline in physical and neurological examinations, and dermatological assessments), extent of exposure, out-of-normal-range laboratory safety test variables, abnormal electrocardiogram (ECG) findings,

out-of-range vital signs, suicidality, and results of the sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, safety magnetic resonance imaging (MRI), vital sign measurements, and cognitive decline assessment such as CogState Brief Battery (CBB) will be summarized by treatment group using descriptive statistics.

APPENDIX 2: E2609-G000-301

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 Version 2.0, dated 06 February 2017

This is a Phase 3, 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in early Alzheimer's disease (EAD) including MCI due to 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, the 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 Extension Phase will continue until commercial availability of E2609, or until a positive risk-benefit assessment in this indication is not demonstrated.

Following completion of the Pre-randomization Phase (up to 50 days plus an additional 30 days if required), and eligibility confirmed by all screening assessments, approximately 1330 subjects will be randomized (1:1), in a double-blind manner, to receive either placebo or E2609 50 mg daily for 24 months. Randomization will be stratified in order to ensure that no more than approximately 25% of the randomized subjects are diagnosed with the early stages of mild dementia due to AD. 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).

The primary objective 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. Secondary objectives include:

- The evaluation of the safety, tolerability, and PK of E2609
- To determine whether E2609 is superior to placebo in EAD subjects on:
    - The time to worsening of CDR scores
    - The time to conversion to dementia for those not clinically staged at baseline as having dementia
    - The rate of change over time based on CDR-SB score over 24 months
    - Selected cognition assessments and questionnaires
- To evaluate clinical changes at 24 months, changes in biomarkers that reflect disease, and MRI at 24 months

The DSMB will conduct an initial unblinded safety review at approximately three (3) to four (4) months from the date the first subjects was randomized. The DSMB will be asked to review the cumulative safety data up to the date identified and provide recommendations to Eisai if the trial

is safe to proceed unchanged or how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. The frequency of subsequent safety reviews will be re-evaluated by the DSMB and Eisai after the initial unblinded safety review.

Safety analysis parameters summarized by treatment group include the incidence of AEs, extent of exposure, out-of-normal-range laboratory safety test variables, abnormal electrocardiogram (ECG) findings, out-of-range vital signs, suicidality, along with the change from baseline in laboratory safety test variables, ECGs, and vital sign measurements.

APPENDIX 3: E2609-G000-302

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

Version 2.0, dated 06 February 2017

This is a Phase 3, 24-month treatment, multicenter, double-blind, placebo-controlled, parallel-group study in early Alzheimer's disease (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, the 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 Extension Phase will continue until commercial availability of elenbecestat (E2609), or until a positive risk-benefit assessment in this indication is not demonstrated.

Following completion of the Pre-randomization Phase (up to 50 days plus an additional 30 days if required), and eligibility confirmed by all screening assessments, a total of 1330 subjects will be randomized (approximately 1:1), in a double-blind manner, to receive either placebo or elenbecestat (E2609) 50 mg daily for 24 months. Randomization will be stratified according to region, 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. 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).

The primary objective 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. Secondary objectives include:

- The evaluation of the safety and tolerability of elenbecestat (E2609)
- To determine whether elenbecestat (E2609) is superior to placebo in EAD subjects on:
    - The time to worsening of CDR scores
    - The time to conversion to dementia for those not clinically staged at baseline as having dementia
    - The rate of change over time (mean slope) based on CDR-SB score over 24 months
    - The change from baseline in CDR-SB at 27 months
    - Selected cognition assessments and questionnaires

- To evaluate the relationship between clinical changes at 24 months and changes in biomarkers reflecting disease progression, amyloid PET, volumetric MRI and functional MRI at 24 months.

The DSMB will conduct an initial unblinded safety review at approximately three (3) to four (4) months from the date the first subject was randomized. The DSMB will be asked to review the cumulative safety data up to the date identified and provide recommendations to Eisai if the trial is safe to proceed unchanged or how to proceed. The study will proceed, including randomization of additional subjects, during DSMB safety reviews. The frequency of subsequent safety reviews will be re-evaluated by the DSMB and Eisai after the initial unblinded safety review.

Safety analysis parameters summarized by treatment group include the incidence of AEs, extent of exposure, out-of-normal-range laboratory safety test variables, abnormal electrocardiogram (ECG) findings, out-of-range vital signs, suicidality, and results of sleep questionnaire, along with the change from baseline in laboratory safety test variables, ECGs, and vital sign measurements. The results of some of the immunologic assessments will be provided to the DSMB for periodic review during the study.

APPENDIX 4: CHARTER SIGNATURE PAGE TEMPLATE

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

E2609-G000-301

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

E2609-G000-302

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

Member Information
Role: DSMB (Chair/Member)
Name:
Affiliation:
I have reviewed the DSMB Charter (*indicate Version number and date)* **for the above studies and approve it as written. I understand my role as a member of this DSMB.** **Signature: _____ Date: _____**

Due to the geographically dispersed DSMB, a separate signature page was created for each member.

APPENDIX 5: DOCUMENT DESTRUCTION STATEMENT TEMPLATE

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

☐ Pre-study notification - Any documents containing unblinded information provided for DSMB review which are downloaded from the secure website or provided via password protected email are to be destroyed or deleted following each meeting.

☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

_____	_____	_____ *(date)*
_____	_____	_____ *(date)*
_____	_____	_____ *(date)*
_____	_____	_____ *(date)*
_____	_____	_____ *(date)*

PPD

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

☒ Pre-study notification - Any documents containing unblinded information provided for DSMB review which are downloaded from the secure website or provided via password protected email are to be destroyed or deleted following each meeting.

☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

PPD

_____	30-MAR-2017 (date)
_____	_____ (date)
_____	_____ (date)
_____	_____ (date)
_____	_____ (date)

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

☒ Pre-study notification - Any documents containing unblinded information provided for DSMB review which are downloaded from the secure website or provided via password protected email are to be destroyed or deleted following each meeting.

☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

PPD

30-MAR-2017
(date)

(date)

(date)

(date)

4/3/17
(date)

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

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☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

PPD

_____	30-MAR-2017 (date)
_____	_____ (date)
_____	30-MAR-2017 (date)
_____	_____ (date)
_____	_____ (date)

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

☒ Pre-study notification - Any documents containing unblinded information provided for DSMB review which are downloaded from the secure website or provided via password protected email are to be destroyed or deleted following each meeting.

☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

PPD

30-MAR-2017
(date)

April 11, 2017
(date)

(date)

(date)

(date)

E2609 Program DSMB

E2609-G000-202

E2609-G000-301

E2609-G000-302

Data Safety Monitoring Board

Document Destruction Statement

☒ Pre-study notification - Any documents containing unblinded information provided for DSMB review which are downloaded from the secure website or provided via password protected email are to be destroyed or deleted following each meeting.

☐ End of study confirmation - all confidential study-related material remaining in my possession have been destroyed.

PPD

		30-MAR-2017 (date)
		(date)
		(date)
		4/3/2017 (date)
		(date)

APPENDIX 6: DSMB RECOMMENDATION FORMS

E2609-G000-202

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: _____ **DSMB Chair:** _____

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☐ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☐ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☐ **No** ☐
Recommendations:	
Comments:	
Eisai Response ***(attach supplementary documents if necessary):*** **Eisai Signature:**_____ **Date:**_____	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☐ **No** ☐

_____ _____

Chair Signature **Date**

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: _____ **DSMB Chair:** _____

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☐ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☐ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☐ **No** ☐
Recommendations:	
Comments:	
Eisai Response ***(attach supplementary documents if necessary):*** **Eisai Signature:**_____ **Date:**_____	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☐ **No** ☐

_____ _____

Chair Signature **Date**

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: _____ **DSMB Chair:** _____

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☐ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☐ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☐ **No** ☐
Recommendations:	
Comments:	
Eisai Response ***(attach supplementary documents if necessary):*** **Eisai Signature:**_____ **Date:**_____	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☐ **No** ☐

_____ _____

Chair Signature **Date**

APPENDIX 7: DSMB MEMBER ROSTER

Data Safety Monitoring Board Members			
Title	**Name/Affiliation**	**Address**	**Telephone number/ E-mail**
PPD			

APPENDIX 8: ABBREVIATIONS

AD	Alzheimer's Disease
CBB	CogState Brief Battery
CDR-SB	Clinical Dementia Rating - Sum Of Boxes
CIOMS	Council for International Organizations of Medical Sciences
COI	Conflict of Interest
CRO	Contract Research Organization
CSF	Cerebrospinal Fluid
CV	Curriculum Vitae
DCS	PPD Data Safety Monitoring Board Coordination Staff
DSMB	Data Safety Monitoring Board
E2609	Elenbecestat
EAD	Early Alzheimer's Disease
ECG	Electrocardiogram
EDC	Electronic Data Capture
IB	Investigator Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISLT	International Shopping List Task
IWRS	Interactive Web Response System
MCI	Mild Cognitive Impairment
MRI	Magnetic Resonance Imaging
PD	Pharmacodynamic
pINN	Proposed International Nonproprietary Name
PK	Pharmacokinetic
PPD	Pharmaceutical Product Development, Inc.
PVG	Pharmacovigilance
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
TLF	Tables, Listings, and Figures

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

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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

E2609-G000-302

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

Member Information

Role: DSMB Chair

Name: PPD

Affiliation: PPD

I have reviewed the DSMB Charter, Version 1.0, dated 27Feb17, for the above studies and approve it as written. I understand my role as the Chair of this DSMB.

Signature: PPD **Date:** 30-MAR-17

PPD

Due to the** **aphically dispersed DSMB, a separate signature page was created for each member.

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

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E2609-G000-302

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

Member Information

Role: DSMB Member

Name: PPD

Affiliation: PPD

I have reviewed the DSMB Charter, Version 1.0, dated 27Feb17, for the above studies and approve it as written. I understand my role as a member of this DSMB.

Signature: PPD **Date:** April 11, 2017

Due to the geographically dispersed DSMB, a separate signature page was created for each member.

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

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E2609-G000-302

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

Member Information

Role: DSMB Member

Name: PPD

Affiliation: PPD

I have reviewed the DSMB Charter, Version 1.0, dated 27Feb17, for the above studies and approve it as written. I understand my role as a member of this DSMB.

Signature: PPD **Date:** 4/3/2017

Due to the geographically dispersed DSMB, a separate signature page was created for each member.

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

E2609-G000-301

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E2609-G000-302

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

Member Information

Role: DSMB Member

Name: PPD

Affiliation: PPD

I have reviewed the DSMB Charter, Version 1.0, dated 27Feb17, for the above studies and approve it as written. I understand my role as a member of this DSMB.

Signature: PPD **Date:** 4/3/17

Due to the geographically dispersed DSMB, a separate signature page was created for each member.

E2609-G000-202

A Placebo-Controlled, Double-Blind, Parallel-Group, Randomized, Dose-Finding Study to Evaluate the Safety and Tolerability of E2609 in Subjects With Mild Cognitive Impairment due to Alzheimer's Disease (Prodromal Alzheimer's Disease) and Mild Dementia Due to Alzheimer's Disease

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E2609-G000-302

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

Member Information

Role: DSMB Member

Name: PPD

Affiliation: PPD

I have reviewed the DSMB Charter, Version 1.0, dated 27Feb17, for the above studies and approve it and understand my role as a member of this DSMB.

PPD

PPD

Signature: _____ **Date:** 30-Mar-2017

Due to the geographically dispersed DSMB, a separate signature page was created for each member.

27 February ~~2016~~ 2017

PPD 12Apr17

Appendix 9: Interim Cognitive Safety Assessment for Elenbecestat (E2609) Studies E2609-G000-301 and E2609-G000-302

Cognitive Safety Assessments will be performed as part of the safety review described in the DSMB Charter. **These analyses are not intended for determining the efficacy or futility of Elenbecestat.**

The cognitive safety analysis will assess cognitive safety starting November 2018. Subsequent analyses will be performed at the data cutoff date for each scheduled safety review. Analyses at the month-6, month-12, month-18 and month-24 visits will be performed once ≥ 100 subjects from each treatment arms (in the pooled arms after combining the two studies) has completed the 6, 12, 18 and 24 month visits, respectively, prior to or on the date of data cutoff for each scheduled safety review. For the September 2019 DSMB, those analyses will be performed regardless of sample size and provided at the study level and then combining the two studies.

DSMB has requested conditional power for September DSMB. Conditional probability of cognitive worsening as well as conditional power will be calculated. Conditional probability of cognitive worsening will be calculated at all visits. Conditional power will be calculated at month-18 and at month-24 visits to give better perspective on the overall safety profile.

When evaluating the results, it is important to note that the cognitive stabilization (or treatment effect) in these patients is expected to begin later in the study (12-24 months). It may require 18 to 24 months for a BACE inhibitor to show any beneficial treatment effect. It is possible that a BACE inhibitor (like Amaranth study for Lanabecestat) could show lack of efficacy rather than cognitive worsening. Finding an enriched subgroup with beneficial treatment effect will be huge in this patient population with numerous failures in the last 15 years. Thus, all these analyses (including additional subgroup analyses) are being provided to help DSMB understand the results on cognitive safety.

Cognitive worsening criteria based on 80% confidence intervals is defined below. With small sample size, even when the mean treatment effect is better than placebo, conditional power will be very small (see simulation results in Appendix 9.1 below). Based on simulations (see Appendix 9.1 below), under null hypothesis (no difference between Elenbecestat and placebo), conditional power will be less than 3% and probability of cognitive worsening will be less than 10%. Thus, if the 80% cognitive worsening criteria (as defined below), is not met, criteria for conditional power evaluation should include

- Mean of Elenbecestat is worse than mean of placebo at a visit ; AND
- Conditional power is less than 3%; AND
- Conditional probability of cognitive worsening is greater than 10%

This criteria can be applied across visits, in pooled studies, by study and across the key subgroups defined below. Determination of cognitive worsening based on totality of data would ensure safety of patients without unduly impacting data integrity of the Mission AD studies.

Criteria for significant cognitive worsening are defined as follows:

An Analysis of Covariance (ANCOVA) model will be used to estimate the change from baseline for the Elenbecestat 50 mg group minus the change from baseline for the Placebo group using an 80% confidence interval (CI). The ANCOVA model will include the baseline variable as a covariate, with treatment group, ApoE4 status, and randomization stratification variables as factors. The analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The observations after discontinuation from study drug will be included in the analyses.

- For the ADAS-cog 11: If the difference between the Elenbecestat 50 mg and the Placebo group is positive and the lower bound of 80% Cl is also positive (i.e. Cl does not include 0), then the criterion for significant cognitive worsening has been reached.
- For the CDR-SB: If the difference between Elenbecestat 50 mg and Placebo is positive and the lower bound of 80% Cl is also positive (i.e. Cl does not include 0), then the criterion for significant cognitive worsening has been reached.

Analyses will be conducted as follows:

1. Unblinded data for the ADAS-cog and CDR-SB will be transferred to the independent statistical group (i.e. Accenture) at defined time points
2. Accenture will perform analysis of the ADAS-cog 11 using programs generated by Eisai
3. The unblinded non-voting Independent Statistician will review the result of the ADAS-cog 11 analysis
    - The Independent Statistician will notify the DSMB that the ADAS-cog 11 did or did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for the ADAS-cog 11 will be provided to the DSMB by the Independent Statistician. The baseline covariate estimate and its significance level will also be included.
    - Listing for the subjects who are included in the summary table but not in the ANCOVA table at specific visit and listing of ADAS-cog11 for discontinued subjects will also be provided to the DSMB by the Independent Statistician.
    - As sensitivity analysis, the same ANCOVA model with multiple imputation for the subjects who would have completed the specific visit will be used to estimate the change from baseline for the Elenbecestat 50 mg group minus the change from baseline for the Placebo group using an 80% CI. Missing data will be imputed using a regression approach. The regression model for imputation will include all subject's observations before study withdrawal and specific visit,

adjusted for treatment group. This imputation approach will reserve the trend in each treatment group (eg, the worsening trend of Elenbecestat group if that is the case) while accounting for the individual subject status before study withdrawal by including the subject's last available observation.

- To calculate conditional probability of cognitive worsening, the same ANCOVA model (no imputation for the subjects who completed the specific visit and multiple imputation for the subjects who would have completed the specific visit) will be used. Missing data will be imputed using a regression approach. The regression model for imputation will include all patient's observations before study withdrawal and specific visit, adjusted for treatment group. This imputation approach will reserve the trend in each treatment group (eg, the worsening trend of Elenbecestat group if that is the case) while accounting for the individual patient status before study withdrawal by including the patient's last available observation.

4. Accenture will then perform the analysis of the CDR-SB
    - Accenture will perform analyses for the CDR-SB using the program generated by Eisai
    - The Independent Statistician will review the CDR-SB results and inform the DSMB that
        - The CDR-SB met or did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for CDR-SB will be provided to the DSMB by the Independent Statistician. The baseline covariate estimate and its significance level will also be included.
    - Listing for the subjects who are included in the summary table but not in the ANCOVA table at specific visit and listing of CDR-SB for discontinued subjects will also be provided to the DSMB by the Independent Statistician.
    - As sensitivity analysis, the same ANCOVA model with multiple imputation for the subjects who would have completed the specific visit will be used to estimate the change from baseline for the Elenbecestat 50 mg group minus the change from baseline for the Placebo group using an 80% CI. Missing data will be imputed using a regression approach. The regression model for imputation will include all subject's observations before study withdrawal and specific visit, adjusted for treatment group. This imputation approach will reserve the trend in each treatment group (eg, the worsening trend of Elenbecestat 50 mg group if that is the case) while accounting for the individual subject status before study withdrawal by including the subject's last available observation.
    - To calculate the conditional probability of cognitive worsening and conditional power of statistically significant improvement on Elenbecestat compared to

placebo (only for 18 and 24 months), the same ANCOVA models (no imputation for the subjects who completed the specific visit and multiple imputation for the subjects who would have completed the specific visit) will be used. Missing data will be imputed using a regression approach. The regression model for imputation will include all patient's observations before study withdrawal and specific visit, adjusted for treatment group. This imputation approach will reserve the trend in each treatment group (eg, the worsening trend of Elenbecestat group if that is the case) while accounting for the individual patient status before study withdrawal by including the patient's last available observation.

5. If the conditional power is too low for both the studies, DSMB will also evaluate the following five subgroups:
    - APOE4 carriers and non-carriers
    - MCI and mild AD
    - Very mild subjects (1) baseline CDR-SB$\leq$1.5); and (2) MMSE $\geq$ 27

The DSMB will determine appropriate recommendation(s) for the studies – an ad hoc meeting for the DSMB may take place as necessary. The DSMB will communicate their recommendation(s) to Eisai regarding the studies as part of the standard program review.

Note: Accenture is external programming group supporting the Independent unblinded DSMB statistician.

Appendix 9.1. Elenbecestat (E2609) studies E2609-G000-301 & E2609-G000-302: Simulation results for Conditional Power

Table 1. **Conditional probability of concluding significant cognitive worsening** at the final analysis given observed interim data $Z(t)$. High conditional power means Elenbecestat 50 mg is cognitively worse than placebo.

Outcome per Observed Interim Data		DSMB Review Timing (% of Subjects)					
		5% Subjects (Sept 2019)	10% Subjects	20% Subjects	30% Subjects	50% Subjects	80% Subjects
Cognitive worsening is NOT observed (Z(t) < 1.28)	Prob (Z(1) > 1.28 | Z(t) = -1)	<0.0001	<0.0001	<0.0001	0.01%	0.01%	<0.0001
	Prob (Z(1) > 1.28 | Z(t) = -0.5) - % improvement	0.02%	0.13%	0.37%	0.44%	0.25%	<0.0001
	Prob (Z(1) > 1.28 | Z(t) =0) - No Treatment Difference	9.45%	8.86%	7.62%	6.30%	3.51%	0.21%
	Prob (Z(1) > 1.28 | Z(t) =0.5)	83.67%	62.45%	42.82%	33.04%	20.89%	5.35%
	Prob (Z(1) > 1.28 | Z(t) =1.00)	99.95%	97.64%	85.74%	74.29%	57.53%	35.86%
	Prob (Z(1) > 1.28 | Z(t) =1.20)	>99.99%	99.60%	94.17%	86.19%	72.23%	55.48%
	Prob (Z(1) > 1.28 | Z(t) =1.27)	>99.99%	99.80%	95.94%	89.28%	76.72%	62.28%
Cognitive worsening is observed (Z(t) > 1.28)	Prob (Z(1) > 1.28 | Z(t) =1.29)	>99.99%	99.84%	96.36%	90.06%	77.93%	64.16%
	Prob (Z(1) > 1.28 | Z(t) =1.39)	>99.99%	99.95%	97.95%	93.36%	83.39%	73.00%

Note: Highlighted areas indicate the column applying to September DSMB.
Cognitive worsening is defined as the lower bound of 80% CI > 0, which is equivalent to z-statistic > 1.28.

Table 2. **Conditional power** of seeing a statistically significant result (Elenbecestat 50 mg better than placebo significantly) at the final analysis given observed interim data $Z(t)$. High conditional power means higher probability that Elenbecestat 50 mg is statistically significantly better than placebo on cognitive endpoints

Interim Observed Z(t)	DSMB Review Timing (% of Subjects)					
	5%	10%	20%	30%	50%	80%
-0.50	61.15%	34.48%	17.33%	10.54%	3.82%	0.09%
0.00	2.22%	1.94%	1.42%	0.96%	0.28%	<0.0001
1.20	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
1.29	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Table 3. **Conditional power** of seeing a statistically significant result (Elenbecestat 50 mg better than placebo significantly) at the final analysis given observed different degree of worsening at interim in 301 (N=1169). High conditional power means higher probability that Elenbecestat 50 mg is statistically significantly better than placebo on cognitive endpoints

% improvement or worsening Observed at Interim	DSMB Review Timing (% of Subjects)					
	5% (September 2019)	10%	20%	30%	50%	80%
-25% (improvement)	96.87%	97.22%	97.88%	98.50%	99.49%	>99.99%
-10%	27.96%	27.43%	26.23%	24.82%	21.04%	10.16%
-5%	9.41%	8.82%	7.58%	6.27%	3.49%	0.21%
0% - No Treatment Difference	2.22%	1.94%	1.42%	0.96%	0.28%	<0.0001
5%	0.38%	0.30%	0.18%	0.09%	0.01%	<0.0001
10%	0.05%	0.03%	0.02%	0.01%	<0.0001	<0.0001
25% (worsening)	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

Note: Highlighted areas indicate the column applying to September DSMB.

Table 3b. Test Statistic Z(t) corresponding to Table 3.

% improvement or worsening Observed at Interim	DSMB Review Timing (% of Subjects)					
	5%	10%	20%	30%	50%	80%
-25% (improvement)	-0.84416	-1.19383	-1.68833	-2.06777	-2.66948	-3.37666
-10%	-0.31101	-0.43983	-0.62202	-0.76181	-0.98349	-1.24403
-5%	-0.15152	-0.21428	-0.30303	-0.37114	-0.47914	-0.60607
0%	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
5%	0.14413	0.20382	0.28825	0.35303	0.45577	0.57650
10%	0.28139	0.39794	0.56278	0.68926	0.88983	1.12555
25% (worsening)	0.65657	0.92853	1.31314	1.60827	2.07626	2.62629

Appendix 9: Interim Cognitive Safety Assessment for Elenbecestat (E2609) Studies E2609-G000-301 and E2609-G000-302

Cognitive Safety Assessments will be performed as part of the safety review described in the DSMB Charter. These analyses are not intended for determining the efficacy or futility of elenbecestat; futility analysis for both the elenbecestat E2609-G000-301 and E2609-G000-302 studies will be carried out as described in the respective protocols.

The first cognitive safety analysis will be performed as an ad hoc analysis. This initial analysis will assess cognitive safety in approximately 200 subjects from each treatment arm focusing on the month-6 visit. Protocols 301 and 302 will be combined.

Subsequent analyses will be performed at the data cutoff date for each scheduled safety review. Additionally, analyses at the month-12, month-18 and month-24 visits will be performed once ≥ 100 subjects from each treatment arms has completed the 12, 18 and 24 month visits, respectively, prior to or on the date of data cutoff for each scheduled safety review.

Criteria for significant cognitive worsening are defined as follows:

An Analysis of Covariance (ANCOVA) model will be used to estimate the change from baseline for the Elenbecestat 50 mg group minus the change from baseline for the Placebo group using an 80% confidence interval (CI). The ANCOVA model will include the baseline variable as a covariate, with treatment group, ApoE4 status, and randomization stratification variables as factors. The analysis will be based on an intent to treat philosophy without regard to adherence to treatment. The observations after discontinuation from study drug will be included in the analyses.

- For the ADAS-cog 11: If the difference between the Elenbecestat 50 mg and the Placebo group is positive and the lower bound of 80% CI is also positive (i.e. CI does not include 0), then the criterion for significant cognitive worsening has been reached.
- For the CDR-SB: If the difference between Elenbecestat 50 mg and Placebo is positive and the lower bound of 80% CI is also positive (i.e. CI does not include 0), then the criterion for significant cognitive worsening has been reached.

Analyses will be conducted as follows:

1. Unblinded data for the ADAS-cog and CDR-SB will be transferred to the independent statistical group (i.e. Accenture) at defined time points
2. Accenture will perform analysis of the ADAS-cog 11 using programs generated by Eisai
3. The unblinded non-voting Independent Statistician will review the result of the ADAS-cog 11 analysis
    - The Independent Statistician will notify the DSMB that the ADAS-cog 11 did or did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for the ADAS-cog 11 will be provided to the DSMB by the Independent

Statistician. The baseline covariate estimate and it's significance level will also be included.

- Listing for the subjects who are included in the summary table but not in the ANCOVA table at specific visit and listing of ADAS-cog11 for discontinued subjects will also be provided to the DSMB by the Independent Statistician.

4. Accenture will then perform the analysis of the CDR-SB
    - Accenture will perform analyses for the CDR-SB using the program generated by Eisai
    - The Independent Statistician will review the CDR-SB results and inform the DSMB that
        - The CDR-SB met or did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for CDR-SB will be provided to the DSMB by the Independent Statistician. The baseline covariate estimate and it's significance level will also be included.
    - Listing for the subjects who are included in the summary table but not in the ANCOVA table at specific visit and listing of CDR-SB for discontinued subjects will also be provided to the DSMB by the Independent Statistician.
    - The DSMB will determine appropriate recommendation(s) for the studies – an ad hoc meeting for the DSMB may take place as necessary
    - The DSMB will communicate their recommendation(s) to Eisai regarding the studies as part of the standard program review

Appendix 9: Interim Cognitive Safety Assessment for Elenbecestat (E2609) Studies E2609-G000-301 and E2609-G000-302

Cognitive Safety Assessments will be performed as part of the safety review described in the DSMB Charter. These analyses are not intended for determining the futility of elenbecestat; futility analysis for both the elenbecestat E2609-G000-301 and E2609-G000-302 studies will be carried out as described in the respective protocols.

The first cognitive safety analysis will be performed as an ad hoc analysis. This initial analysis will assess cognitive safety in approximately 200 subjects from each treatment arm focusing on the month-6 visit.

Subsequent analyses will be performed at the data cutoff date for each scheduled safety review. Additionally, analyses at the month-12, month-18 and month-24 visits will be performed once ≥ 100 subjects from each treatment arms has completed the 12, 18 and 24 month visits, respectively, prior to or on the date of data cutoff for each scheduled safety review.

Criteria for significant cognitive worsening are defined as follows:

An Analysis of Covariance (ANCOVA) model will be used to estimate the change from baseline for the Elenbecestat 50 mg group minus the change from baseline for the Placebo group using an 80% confidence interval (CI). The ANCOVA model will include the baseline variable as a covariate, with treatment group, ApoE4 status, and randomization stratification variables as factors.

- For the ADAS-cog 11: If the difference between the Elenbecestat 50 mg and the Placebo group is positive and the lower bound of 80% CI is also positive (i.e. CI does not include 0), then the criterion for significant cognitive worsening has been reached.
- For the CDR-SB: If the difference between Elenbecestat 50 mg and Placebo is positive and the lower bound of 80% CI is also positive (i.e. CI does not include 0), then the criterion for significant cognitive worsening has been reached.

Analyses will be conducted in the order as described in Figure1 and as follows:

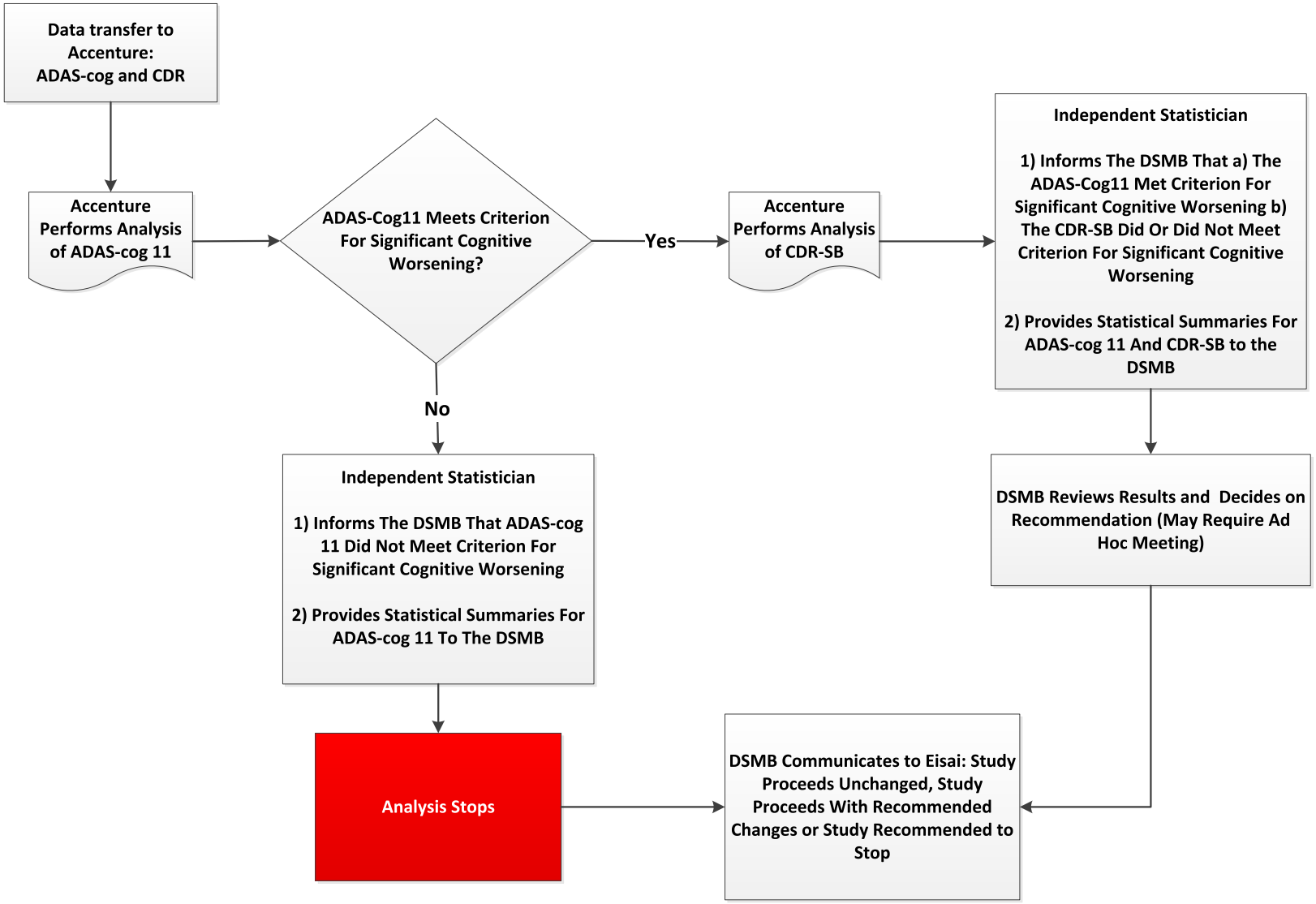
1. Unblinded data for the ADAS-cog and CDR-SB will be transferred to the independent statistical group (i.e. Accenture) at defined time points
2. Accenture will perform analysis of the ADAS-cog 11 using programs generated by Eisai
3. The unblinded non-voting Independent Statistician will review the result of the ADAS-cog 11 analysis
4. If the ADAS-cog 11 does not meet the criterion for significant cognitive worsening:
    - The Independent Statistician will notify the DSMB that the ADAS-cog 11 did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for the ADAS-cog 11 will be provided to the DSMB by the Independent Statistician
    - No additional analyses will be performed

- The DSMB will communicate their recommendation to Eisai as part of the standard program review

5. If the ADAS-cog 11 meets the criterion for significant cognitive worsening, the Independent Statistician will instruct Accenture to perform the analysis of the CDR-SB
    - Accenture will perform analyses for the CDR-SB using the program generated by Eisai
    - The Independent Statistician will review the CDR-SB results and inform the DSMB that
        - The ADAS-Cog 11 met criterion for significant cognitive worsening
        - The CDR-SB met or did not meet the criterion for significant cognitive worsening
    - Statistical summaries (mean, SD, LS mean & SE as well as the 80% confidence interval) for the ADAS-cog 11 and CDR-SB will be provided to the DSMB by the Independent Statistician
    - The DSMB will determine appropriate recommendation(s) for the studies – an ad hoc meeting for the DSMB may take place as necessary
    - The DSMB will communicate their recommendation(s) to Eisai regarding the studies as part of the standard program review

Appendix 9: Interim Cognitive Safety Assessment for Elenbecestat (E2609) Studies E2609-G000-301 and E2609-G000-302

Figure 1 Cognitive Safety Analyses



Eisai E2609 BEAM Program
DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 11 September 2019 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☐ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☒ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☐ **No** ☒
Recommendations:	
Comments: The DSMB recommends stopping the study due to an unfavorable risk-benefit ratio. For those on active drug treatment, there is no evidence of potential efficacy and the adverse event profile is worse than placebo. The DSMB believes that the safety risk outweighs any potential benefit for patients continuing in this trial. Concerning cognitive safety, the DSMB sees evidence of detrimental trends for subjects on active treatment on some cognitive measures by 18 months. Additionally, at 24 months there is a more consistent negative safety trend.	
Eisai Response *(attach supplementary documents if necessary):* **Eisai Signature:** PPD **Date:** 9/18/19	
Each DSMB mer[illegible] has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☒ **No** ☐

PPD

Chair Signature

9/11/2019

Date

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 27 Mar 2019 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☐ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☒ **No** ☐
Recommendations: 1. **The DSMB would like a follow up meeting on or before August 1st** 2. **The DSMB would like some additional follow up analyses prior to this meeting; the details will be discussed with the unblinded statistician**	
Comments:	
Eisai Response ***(attach supplementary documents if necessary):*** **Eisai Signature:** PPD **Date:**	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☒ **No** ☐

PPD

ure

3/28/2019

Date

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 27 Mar 2019 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ **Yes**
Study continuation with modification	☐ **Yes** *(Specify under recommendations)*
Study termination	☐ **Yes**
Is additional follow up requested? *(Specify under recommendations)*	**Yes** ☒ **No** ☐

Recommendations:

1. **The DSMB would like a follow up meeting on or before August 1st**
2. **The DSMB would like some additional follow up analyses prior to this meeting; the details will be discussed with the unblinded statistician**

Comments:

Eisai Response ***(attach supplementary documents if necessary):***

PPD

Eisai Signature:_____ **Date:**_____

Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	**Yes** ☒ **No** ☐

PPD

_____ 3/28/2019

ature **Date**

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 10 Dec 2018 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☐

Recommendations:

1. DSMB would like to examine CDR-SB scores in concert with ADAS-Cog to assess cognitive safety
2. Eisai have employed performance on the Digit Cancellation test as a cognitive safety measure. The DSMB feels would it be helpful to determine from other sponsors with BACE inhibitor data whether they included this measure, and if so whether it was sensitive to cognitive change. If Eisai can gather this data from their industry colleagues, it would be appreciated.

Comments:

PPD

Eisai Response (a plementary documents if necessary):

Eisa PPD Date: December 17, 2018

Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

12/13/2018
Date

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 10 Dec 2018 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☐
Recommendations:	
Comments: 1. DSMB would like to examine CDR-SB scores in concert with ADAS-Cog to assess cognitive safety 2. Eisai have employed performance on the Digit Cancellation test as a cognitive safety measure. The DSMB feels would it be helpful to determine from other sponsors with BACE inhibitor data whether they included this measure, and if so whether it was sensitive to cognitive change. If Eisai can gather this data from their industry colleagues, it would be appreciated.	
Eisai Response *(plementary documents if necessary):* **Eisai Signature:** PPD PPD December 17 2018	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

12/13/2018
Date

E2609-G000-202
E2609-G000-301
E2609-G000-301
DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 07 September 2018 DSMB Chair: PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☐

Recommendations:

1. The DSMB recommends that both Phase 3 studies as well as the Phase 2 OLE continue unchanged.
2. The DSMB agrees with proposal for decreasing collection of PBMCs
3. The DSMB DSMB agrees with proposal to stop lymphocyte subset testing in new subjects and completing data collection in ongoing subjects out to 1 year
4. Given the recent Verubecastat information, Eisai proposed a Cognitive Safety Analysis with a boundary reached if E2609 is at least 50% worse than Placebo in ADAS-Cog11 at the 6 Month visit. The DSMB appreciated a Cognitive Safety look, but did not like the vagueness of "50% worse" approach and proposes a confidence interval (CI) approach to determining when a boundary has been reached. A statistical analysis of ADAS-cog11 will estimate change from baseline E2609 minus change from baseline Placebo, where a positive point estimate occurs when the E2609 ADAS-cog11 is worse than Placebo at month 6, 12, 18 or 24. If the lower bound of the CI is positive (i.e. CI does not include 0) then the boundary is reached and a full analysis of the primary efficacy parameter is conducted and shared with the DSMB. Using an 80% CI allows the bound to be reached before the ADAS-cog11 of E2609 is considered statistically significantly worse than Placebo at a stricter level of 95% CI.

Comments:
Regarding the T PPD will work with PPD to reformat the AE tables. Additionally, we request a table o ions by SOC/PT by treatment group.

Eisai Response (mentary documents if necessary):

Eisai Signature: PPD Date: September 17 2018

Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

Chair Signature PPD Date 12 SEP 2018

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 23 May 2018 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☐
Recommendations:	
Comments: 1. If available, please provide discontinuation narratives 2. Please provide "spaghetti plots" for patients with certain laboratory abnormalities 3. Please provide additional tabular representation for the results of neuropsychiatric testing par PPD	
Eisai Response *(a plementary documents if necessary):* PPD **Eisai Signature:** PPD NGM PCU **Date:** May 29, 2018	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☑ No ☐

PPD

5/23/18
Date

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 23 May 2018 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☐
Recommendations:	
Comments: 1. If available, please provide discontinuation narratives 2. Please provide "spaghetti plots" for patients with certain laboratory abnormalities 3. Please provide additional tabular representation for the results of neuropsychiatric testing parameters	
Eisai Response *(a[PPD]upplementary documents if necessary):* [PPD] **Eisai Signature:** [PPD] NGM PCU **Date:** May 29, 2018	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☑ No ☐

PPD

5/23/18
Date

Eisai

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 27 February 2018 DSMB Chair: PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒
Recommendations: 3. Going forward, presentation of SAEs will include overview. Individual SAEs to be presented only in cases of IND Safety Alerts or upon DSMB request. 4. TLG changes requested a. NPI scores associated with certain adverse events b. Additional Lymhocyte listings c. TEAE tables need to be adjusted to proper % incidence	
Comments: PPD	
Eisai Response *supplementary documents if necessary):* PPD Eisai Signature PPD NGM PCU Date: March 1 2018	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

3/1/18
Date

Eisai

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 27 February 2018 DSMB Chair: PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒

Recommendations:

5. Going forward, presentation of SAEs will include overview. Individual SAEs to be presented only in cases of IND Safety Alerts or upon DSMB request.
6. TLG changes requested
   a. NPI scores associated with certain adverse events
   b. Additional Lymhocyte listings
   c. TEAE tables need to be adjusted to proper incidence

Comments:

Eisai Response (PPD *plementary documents if necessary):*

Eisai Signature: PPD NGM PCU Date: March 1, 2018

Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

3/1/18
Date

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 20 November 2017 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒
Recommendations:	
Comments: **For presentation of serious or significant events:** • Please include presentation of the NPI scores with subscales for neuropsychicatric events of interest • PPD ort raw values instead of characterizations such as 'increased' or d' for laboratory and other relevant measurements (eg VS, ECG).	
Eisai Response *upplementary documents if necessary):* PPD **Eisai Signatur** PPD **Date:** November 21, 2017	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

11/20/17
Date

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 20 November 2017 DSMB Chair: PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒
Recommendations:	
Comments: For presentation of serious or significant events: • Please include presentation of the NPI scores with subscales for neuropsychicatric events of interest • PPD rt raw values instead of characterizations such as 'increased' or for laboratory and other relevant measurements (eg VS, ECG).	
Eisai Response *pplementary documents if necessary):* Eisai Signature: PPD Date: November 21, 2017	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

11/20/17
Date

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 08 August 2017 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒
Recommendations: None at this time.	
Comments: PPD will work with PPD to see if a more integrated presentation of neuro and cognitive TLGs is possible.	
Eisai Response ***(attach supplementary documents if necessary):*** **Eisai Signature:** PPD **Date:** 14 Aug 2017	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

gnature

8/8/17
Date

E2609-G000-302

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 08 August 2017 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☒ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☒

Recommendations:

None at this time.

Comments:

PPD will work with PPD to see if a more integrated presentation of neuro and cognitive TLGs is possible

Eisai Response ***(attach supplementary documents if necessary):***

Eisai Signature: PPD **Date:** 14 Aug 2017

Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☒ No ☐

PPD

8/9/17
Date

E2609-G000-301

DSMB CHAIR RECOMMENDATION FORM

Date of Meeting: 12 April 2017 **DSMB Chair:** PPD

Based upon the DSMB review of the data provided for this Data Review Meeting, the following decisions and recommendations were agreed upon:	
Study continuation without modification	☑ Yes
Study continuation with modification	☐ Yes *(Specify under recommendations)*
Study termination	☐ Yes
Is additional follow up requested? *(Specify under recommendations)*	Yes ☐ No ☑
Recommendations:	
Comments:	
Eisai Response ***(attach supplementary documents if necessary):***	
Eisai Signature: PPD **Date:** 13 Apr 2017	
Each DSMB member has acknowledged the decision making processes regarding recommendations are based on a comprehensive evaluation of the data presented. The DSMB members offer the above recommendations based upon their review of the data presented; their medical expertise, and their participation in the DSMB meeting. The DSMB members understand that the recommendations are based on a unanimous vote unless otherwise noted.	Yes ☑ No ☐

PPD

12 APR 2017
Date

Eisai

E2609 PROGRAM

E2609-G000-301
E2609-G000-302

DATA SAFETY MONITORING BOARD
DATA REVIEW MEETING MINUTES

Pages 191-333 removed - Out of Scope of phase 1 of Policy 0070 - Data Safety Monitoring Board Data Review Meeting Minutes

DATA INTEGRITY PROTECTION PLAN

Protocol Number: E2609-G000-301

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

Version: V3.0

Date: November 11, 2019

SIGNATURE PAGE

Statistical Lead:

PPD

Signature

Date:

Study Director:

PPD

Signature

Date:

Clinical Operations Lead:

PPD

Signature

Date:

Lead Data Manager:

PPD

Signature

Date:

TABLE OF CONTENTS

ABBREVIATIONS

Abbreviation	Term
ADaM	analysis data model
AE	adverse event
CRF	case report form
CRO	Contract Research Organisation
CSF	cerebrospinal fluid
CSR	clinical study report
DIPP	Data Integrity Protection Plan
DM	Data Management
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
FTP	file transfer protocol
IxRS	Interactive Response System, voice or web
MRI	magnetic resonance imaging
PCU	Product Creation Unit
PET	positron emission tomography
PK	pharmacokinetic
PD	pharmacodynamic
SAE	serious adverse event
SAP	statistical analysis plan
SDTM	Study Data Tabulation Model
SOP	Standard Operating Procedure
SWP	Standard Working Procedure
TLGs	Tables, Listings, Graphs

1 INTRODUCTION

All processes will follow current SOPs and SWPs.

The Core phase of this study is double-blind. The integrity of the data will be ensured by the standard procedures. Activities and access of data before database lock for the core phase of the study are documented below. Open Label Extension treatment data is not blinded to any personel, but any external data will follow the same process described below.

Revision History

Version No.	Summary
1.0	Original version
2.0	Add tau PET and cognitive safety monitoring in DSMB, clarify the process of sensitive transfers , update the process for amyloid PET, describe Open Label Extension data, remove China PK
3.0	Add plasma PD/biomarker CRO, clarify the process for external data in Open Label Extension, add and clarify the members in independent data operation team.

2 PERSONNEL RESPONSIBILITIES

All personnel involved with the study will remain blinded until database lock of the core study, with the following exceptions:

IxRS Vendor: the statisticians and support staff at the independent company responsible for the generation of the randomization schedule and the IxRS system. The project team at the vendor has access to the randomization list showing the treatment assignments.

Eisai Clinical Supply: will have full access to the randomization codes.

PK Vendor: will have full access to the randomization codes.

DSMB: Data Safety Monitoring Board is responsible for monitoring the overall safety of the study at regular intervals and will make recommendations to the Sponsor. DSMB members will be aware of unblinded treatment assignments.

DSMB Support CRO: The independent biostatistics group that is responsible for supplying the study data summaries, by unblinded treatment, for the review by the DSMB. This group includes the DMC support statistician and programmer who will be aware of unblinded treatment assignments. The CRO staff supporting the organization of the DSMB meetings (including the closed sessions) will also be unblinded.

3 INFORMATION MANAGEMENT

The details below only relate to ensuring data integrity. Most of the processes have additional documentation that provides more details.

3.1 Treatment Codes

The treatment allocation randomization is performed by the IxRS vendor statistician. The IxRS vendor will keep the code securely and will not transfer the unblinded code to Eisai until database lock of core study.

Upon signoff of the Randomization Release Code form, the treatment codes will be accessible to the following personnel via secure FTP:

1) The independent DSMB support statistician/programmer prior to the first DSMB meeting

2) PK vendor

3.2 Data Conversion and Transfer

To prevent any potential unblinding prior to database lock of the core study, the following data will be masked by a project independent data operation member at Eisai, the detailed processing can be found in Appendix 1.

- PK
- PD/Biomarker/amyloid PET/tau PET/fMRI/vMRI
- Lymphocyte subset

IxRS randomization treatment codes will be transferred to Eisai's clinical database via sFTP upon database lock of the core study. Upon signoff of the Randomization Release Code form, Eisai Data Ops will transfer the data to SDTM programming team. Before database lock, dummy randomization codes will be used for programming purposes.

3.3 Data Review

Data review will be undertaken following standard approaches, with access to the data as above.

Patient profiles include all available clinical data (see Section 4) except treatment assignment. The outputs can be from either Ongoing Safety Monitoring (OGSM) or Study Quality Surveillance (SQS), and will be provided to the Clinical team members for blinded individual subject review.

3.4 Data Summaries

No summaries or analyses will be provided by unblinded treatment group before database lock of the core study, except as required by DSMB.

3.5 Data Safety Monitoring Board

Once the data for each DSMB meeting have been provided, two sets of reports will be produced:

- Open Reports by dummy treatment group generated by Eisai Biostats (for Sponsor review only)
- Closed Reports by unblinded treatment group generated by DSMB support CRO (for DSMB members only)

The DSMB members will review the closed reports and any relevant documentation. As specified in the DSMB charter, the only recommendation that will be communicated by the DSMB to Eisai will be the recommendation to continue the study without modification, to continue the study with modification or to terminate the study. No detailed statistical results will be shared with Eisai.

3.6 SAE Reporting

Reporting of SAEs and Events of special situations to health authorities, ethics committees, and investigators will be made in compliance with applicable local regulations and SOPs. Treatment information will not be communicated to study team members.

3.7 Development of TLGs

Biostats will have access to blinded SDTM datasets. Biostats will create blinded ADaM datasets from the SDTM datasets. Programs will be developed for all analyses and summaries using the dummy treatment groups, which will be clearly indicated.

4 SUMMARY OF INFORMATION ACCESS

Function	Information Available	Information Excluded
IxRS Vendor	Randomization code IxRS data	Study data
Clinical Supply	Randomization code	Study data
PK Vendor	Randomization code PK data	Clinical data
Clinical Operation	eCRFs Masked external data[1] Blinded patient profiles	IxRS treatment codes
Clinical (Study Director and Medical Monitor)	eCRFs Masked external data[1] Blinded patient profiles	IxRS treatment codes
Data Management	eCRFs Masked external data[1] Blinded Raw data	IxRS treatment codes

SDTM Programmer	Blinded raw data	IxRS treatment codes
Statistician & Statistical Programmer	Blinded SDTM- data	IxRS treatment codes
PK Scientist	Masked PK data	IxRS treatment codes Clinical data
Translational Medicine Expert	Masked PD/Biomarker data	IxRS treatment codes Clinical data[2]
DSMB	Unblinded safety data (including cognitive safety data) Unblinded efficacy data in futility analysis	PK/PD/Biomarker/Efficacy Imaging data
DSMB Support CRO	Unblinded safety data (including cognitive safety data) Unblinded efficacy data in futility analysis	PK/PD/Biomarker/Efficacy Imaging data

[1] Does not include PK, post-baseline PD/Biomarker/amyloid PET/tau PET/fMRI/vMRI and lymphocyte subset data

[2] Except the lymphocyte subset prior to randomization

APPENDIX 1 PROCESSING OF SENSITIVE DATA TRANSFERS

Data Type	Vendor	Processing before Milestone (Dry Run)
Amyloid PET	Bioclinica	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values among all the **post-baseline visits**
Tau PET	Bioclinica	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
fMRI/vMRI	Bioclinica	3) Keep the actual values at Screening/Baseline 4) Scramble the post-baseline values **among all the post-baseline visits**
CSF PD/biomarker	Covance	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
Plasma PD/biomarker	Covance	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
LB (Lymphocyte Subset)	Covance	1) Keep the actual values at Screening and Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
Plasma PD/biomarker	VUmc Research BV	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
Global PK	QPS	1) Two types of data processing: a. For the PK review of PK scientist, replace the actual subject ID with dummy ID b. For the statistical programming work, scramble the values **among all the visits**

Table 1 Data Processing Procedure of Sensitive Data

During Study Conduct

- The Vendors in Table 1 transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data is placed in **"unblind"** subdirectory on sFTP for BEAM 301.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-301\unblind
  Only the vendors in table 1 and the independent Data Ops representatives have read/write access to the folder location.

1. The independent Data Ops representative is notified of the transfer.

2. The independent Data Ops representative:
   - does the necessary data processing as described in Table 1
     AND
   - downloads the processed data as per Table 1 to
     \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw
3. Then the data will be used for Data Cleaning Listings, SDTM mapping and OGSM mapping.

During Milestone (as agreed upon):

- The Vendors in table 1 transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data placed in **"unblind"** subdirectory on sFTP for BEAM 301.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-301\unblind
  Only the vendors in table 1 and the independent Data Ops representatives have read/write access to the folder location.

1. For any agreed upon Milestone (for example, DSMB): the data in Table 1 is transferred by independent Dataops representative from sFTP **"unblind"** subdirectory to

   To the Following Secure Location:
   \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw\unblind

   Only the Independent SDTM Programmer has read access to the folder location above

   AND
   - downloads the latest other external data related to the study (not in the above list) and CRF data from :
     \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw

     Proceeds to create SDTM datasets and runs compliance check on the data.

2. The independent SDTM programmer notifies the independent Biostats programmer of the availability of unprocessed SDTM data under

   \\rigbionn01\saswok\dmprojects\<compound>\<study>\sds\data\unblind

   Only the independent SDTM programmer and the independent Biostats programmer have read/write access to the SDTM data (which includes sensitive data) directory

For DB LOCK

- The Vendors in the table above transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data is placed in **"unblind"** subdirectory on sFTP for BEAM 301.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-301\unblind

Only the venders in the table above and the independent Data Ops representatives have read/write access to the folder location.

1. Upon receiving the signed Randomization Release Form, the data is moved to **\\rigbionn01\saswok\dmprojects\<compound>\<study>\raw** for SDTM mapping and OGSM mapping.

Independent SDTM Programmer	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from Sep 11, 2018)
Independent Biostats Programmer	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from Sep 11, 2018) PPD (from 1st ver. finalization)
Independent Statistician	PPD (from 1st ver. finalization)
Independent Data Ops	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from 1st ver. finalization) PPD (from 1st ver. finalization) PPD (from Sep 11, 2018) PPD (from 1st ver. finalization) PPD (from Nov 5, 2019) PPD (from Nov 5, 2019)

DATA INTEGRITY PROTECTION PLAN

Protocol Number: E2609-G000-302

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Version: V3.0

Date: November 11, 2019

SIGNATURE PAGE

Statistical Lead:

PPD

Signature

Date:

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PPD

Signature

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PPD

Signature

Date:

Lead Data Manager:

PPD

Signature

Date:

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SDTM Programmer	Blinded raw data	IxRS treatment codes
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Plasma PD/biomarker	Covance	1) Keep the actual values at Screening/Baseline 2) Scramble the post-baseline values **among all the post-baseline visits**
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China PK	Frontage	Same as Global PK

Table 1 Data Processing Procedure of Sensitive Data

During Study Conduct

- The Vendors in Table 1 transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data is placed in **"unblind"** subdirectory on sFTP for BEAM 302.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-302\unblind
  Only the vendors in table 1 and the independent Data Ops representatives have read/write access to the folder location.

1. The independent Data Ops representative is notified of the transfer.
2. The independent Data Ops representative:
   - does the necessary data processing as described in Table 1
     AND
   - downloads the processed data as per Table 1 to
     \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw
3. Then the data will be used for Data Cleaning Listings, SDTM mapping and OGSM mapping.

During Milestone (as agreed upon):

- The Vendors in table 1 transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data placed in **"unblind"** subdirectory on sFTP for BEAM 302.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-302\unblind
  Only the vendors in table 1 and the independent Data Ops representatives have read/write access to the folder location.

1. For any agreed upon Milestone (for example, DSMB): the data in Table 1 is transferred by independent Dataops representative from sFTP **"unblind"** subdirectory to

   To the Following Secure Location:
   \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw\unblind

   Only the Independent SDTM Programmer has read access to the folder location above

   AND
   - downloads the latest other external data related to the study (not in the above list) and CRF data from :
     \\rigbionn01\saswok\dmprojects\<compound>\<study>\raw

     Proceeds to create SDTM datasets and runs compliance check on the data.

2. The independent SDTM programmer notifies the independent Biostats programmer of the availability of unprocessed SDTM data under

   \\rigbionn01\saswok\dmprojects\<compound>\<study>\sds\data\unblind

   Only the independent SDTM programmer and the independent Biostats programmer have read/ write access to the SDTM data (which includes sensitive data) directory

For DB LOCK

- The Vendors in the table above transfer the "unblinded" data to Eisai via sFTP protocol on sFTP server. The data is placed in **"unblind"** subdirectory on sFTP for BEAM 302.
  \\RIGVEND01\Accenture\EXTERNAL_DATA\C45P\e2609-G000-302\unblind

Only the venders in the table above and the independent Data Ops representatives have read/write access to the folder location.

1. Upon receiving the signed Randomization Release Form, the data is moved to **\\rigbionn01\saswok\dmprojects\<compound>\<study>\raw** for SDTM mapping and OGSM mapping.

Independent SDTM Programmer	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from Sep 11, 2018)
Independent Biostats Programmer	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from Sep 11, 2018) PPD (from 1st ver. finalization)
Independent Statistician	PPD (from 1st ver. finalization)
Independent Data Ops	PPD (from 1st ver. finalization to Sep 10, 2018) PPD (from 1st ver. finalization) PPD (from 1st ver. finalization) PPD (from Sep 11, 2018) PPD (from 1st ver. finalization) PPD (from Nov 5, 2019) PPD (from Nov 5, 2019)