Official Title: Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Two Year Study to Evaluate the Effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease With Option for up to an Additional Two Years of Treatment and an Open-Label Extension With Active Study Treatment

NCT Number: NCT01224106

Document Date: Protocol Version H: 09-July-2018

CLINICAL STUDY PROTOCOL
PROTOCOL NUMBER WN25203H
RO4909832
EUDRACT NO.: 2010-019895-66
IND 102,266

Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Two Year Study to Evaluate the Effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease with Option for up to an Additional Two Years of Treatment and an Open-Label Extension with Active Study Treatment

PROTOCOL APPROVAL

Protocol Number/Version: WN25203H

Date: See last date in electronic signature manifestation below.

Protocol approved by: See electronic signature manifestation below.

Approver's Name	Title	Date and Time (UTC)
[redacted]	Company Signatory	09-Jul-2018 21:03:07

PROTOCOL AMENDMENT, VERSION H: RATIONALE

Protocol WN25203 has been amended to allow patients to continue receiving open-label gantenerumab until July 2020, at which time anticipated results from other relevant monoclonal antibody treatments targeting amyloid-β will be available. Relevant sections updated include the following:

- Section 1.2.4 (Rationale for Prolonging Open-label Extension [Part 3])
- Section 3.1 (Overview of Study Design and Dosing Regimen)
- Section 5 (Table 9, Schedule of Assessments – Open-Label Extension Years 4 and 5 for Participants Continuing Part 3 until July 2020)
- Section 5.1.6 (Part 3 – the Open-Label Extension)
- Section 5.2 (Assessments and Procedures)
- Section 8.7 (Analysis Considerations for Data Collected during Part 3 – the Open-Label Extension)
- Section 10.1.2 (Independent Data Monitoring Committee)

Additional changes to the protocol are as follows:

- Gantenerumab information has been updated (Section 1.1.2, Gantenerumab)
- An overview the of clinical safety, and pharmacodynamics PET amyloid results from the ongoing open-label Studies WN25203 and WN28745 have been added (Section 1.1.2.4, WN28745; Section 1.1.2.5, WN25203 and WN28745 Open-Label Extension Studies; Section 1.3.2, Reduction in Brain Aβ by Gantenerumab)
- MRI findings have been updated (Section 1.3.3, MRI Findings).
- Section 2.5 (Objectives of Part 3 [Open-Label Extension]) has been updated to clarify which objectives for Part 3 will be evaluated during the initial 3 years of Part 3.
- Observation period after dosing has been adjusted to correspond with Study File Note 14 (Section 5.1.6, Part 3 – the Open-Label Extension)
- Storage parameters of solution at ambient temperature has been adjusted from 6 to 4 hours to correspond with Study File Note 12 (Section 6.3.2, Preparation and Administration of IMP in Part 3)
- Conditions for recording MRI observations has been adjusted to correspond with Study File Note 12 (Section 7.1.4, MRI Observations)
- To further strengthen safety monitoring and reporting, Section 7 (Safety Instructions and Guidance) has been updated to provide clarification on reporting of findings that may result in an adverse event (laboratory abnormalities, vital signs, MRI observations [as indicated above], events associated with overdose or medication error), to provide clarification of deaths to specify events that require immediate reporting to the Sponsor (serious adverse events, adverse events of special interest, pregnancies and medical device complaints), and to provide more information on expedite reporting, on recording of adverse events in the eCRF, and on follow-up of adverse events. The Safety Plan (Section 7.3) has been included to address risks, replacing the warnings and precautions section. The following sections have been clarified or added:
  - Section 7.1.1 (Clinical Adverse Events)

  - Section 7.1.1.1 (Intensity)
  - Section 7.1.1.2 (Drug-Adverse Relationship [Assessment of Causality of Adverse Events])
  - Section 7.1.1.3 (Serious Adverse Events [Immediately Reportable to Sponsor])
  - Section 7.1.1.4 (Adverse Events of Special Interest ([Immediately Reportable to Sponsor])
  - Section 7.1.2 (Laboratory Test Abnormalities)
  - Section 7.1.2.1 (Follow-up of Abnormal Laboratory Tests Values)
  - Section 7.1.3 (Abnormal Vital Sign Values)
  - Section 7.1.5 (Adverse Events Associated with an Overdose or Error in Drug Administration)
  - Section 7.1.6 (Deaths)
  - Section 7.2.2 (Reporting of Serious Adverse Events and Adverse Events of Special Interest [Immediately Reportable])
  - Section 7.2.3 (Reporting of Pregnancy)
  - Section 7.2.4 (Reporting Requirements for Medical Device Complaints)
  - Section 7.2.5 (Expedited reporting to Health Authorities, Investigators, Institutional Review Boards and Ethics Committee)
  - Section 7.2.6 (Recording Adverse Events on the eCRF)
  - Section 7.2.7 (Follow-up of Patients after Adverse Events)
  - Section 7.3 (Safety Plan)
- Protocol deviation assessment and reporting have been clarified (Section 13, Conditions for Modifying the Protocol)

Additional minor changes have been made to improve clarity and consistency. Substantive new information appears in italics. This amendment represents cumulative changes to the original protocol.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF APPENDICES

PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP TWO YEAR STUDY TO EVALUATE THE EFFECT OF SUBCUTANEOUS RO4909832 ON COGNITION AND FUNCTION IN PRODROMAL ALZHEIMER'S DISEASE WITH OPTION FOR UP TO AN ADDITIONAL TWO YEARS OF TREATMENT AND AN OPEN-LABEL EXTENSION WITH ACTIVE STUDY TREATMENT**
PROTOCOL NUMBER:	WN25203
VERSION NUMBER:	H
EUDRACT NUMBER:	2010-019895-66
IND NUMBER:	102,266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], M.D., Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

I agree to conduct the study in accordance with the current protocol.

_____

Principal Investigator's Name (print)

_____ _____

Principal Investigator's Signature Date

Please retain the signed original of this form for your study files. Please return a copy of the signed form as instructed by your local study monitor.

SYNOPSIS OF PROTOCOL NUMBER WN25203H

TITLE	Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Two Year Study to Evaluate the Effect of Subcutaneous RO4909832 on Cognition and Function in Prodromal Alzheimer's Disease with Option for up to an Additional Two Years of Treatment and an Open-Label Extension with Active Study Treatment		
SPONSOR	Roche	Clinical Phase	3
INDICATION	Prodromal Alzheimer's Disease		
OBJECTIVES OF DOUBLE-BLIND PART OF THE STUDY Primary	To evaluate the effect of gantenerumab versus placebo on the change in the Clinical Dementia Rating scale Sum of Boxes (CDR-SOB), a global measure of cognition and functional ability.		
Secondary Cognition, global, and functioning	To evaluate the effect of gantenerumab versus placebo on cognition (assessed with the Alzheimer Disease Assessment Scale-Cognition [ADAS-Cog], Mini Mental State Exam [MMSE], Cambridge Neuropsychological Test Automated Battery [CANTAB], and the Free and Cued Selective Reminding Test-Immediate Recall [FCSRT-IR]) on global measures (based on the CDR global score), and on functioning (assessed with the Functional Activities Questionnaire [FAQ]), on neuropsychiatric functioning (assessed with the Neuropsychiatric Inventory Questionnaire [NPI-Q]) and on time to onset of dementia.		
Safety	To assess the safety and tolerability of gantenerumab assessed by magnetic resonance imaging (MRI), physical and neurological examinations, vital signs, blood and urine safety tests, ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), Geriatric Depression Scale (GDS), and adverse event monitoring.		
MRI volumetry	To evaluate the effect of gantenerumab versus placebo on hippocampal volume, whole brain volume, ventricular enlargement, and possibly other volumetric measures of the brain.		
CSF Biomarkers	To evaluate the effect of gantenerumab versus placebo on levels of cerebrospinal fluid (CSF) biomarkers of Alzheimer's disease (AD) pathology (i.e., total tau [T-tau], phospho-tau [p-tau], and amyloid-beta ($A\beta_{1-42}$]).		
Pharmacokinetics/ Anti-Drug Antibodies	To determine the relationship of plasma and CSF concentrations of gantenerumab on other responses. To assess incidence of anti-gantenerumab antibodies, and if relevant, evaluate its effect on the pharmacokinetic (PK), pharmacodynamic (PD), efficacy. and safety parameters.		
Exploratory Plasma Biomarkers	To evaluate the effect of treatment on peripheral biomarkers of amyloid deposition and/or clearance, neurodegeneration, inflammation, and other markers known to be involved in the pathogenesis of AD.		

Clinical Genotyping	To evaluate the effect of gene encoding apoliprotein E (ApoE) ε4 genotype and fragment crystalizable gamma receptor (FcγR) genotype on PK/PD, efficacy, and safety parameters
OBJECTIVES OF THE OPEN-LABEL EXTENSION - PART 3	
Primary: Safety:	To assess short-term and long-term safety and tolerability of gantenerumab (RO4909832) given at doses up to 1200 mg subcutaneous (SC) every 4 weeks (Q4W) by MRI, physical and neurological examinations, vital signs, blood safety tests, ECGs, C-SSRS, and adverse event monitoring.
Secondary: Brain MRI Volumetry	To evaluate the effect of gantenerumab over time on hippocampal volume, whole brain volume, ventricular enlargement, and possibly other volumetric measures of the brain compared to baseline and to the start of Part 3
Brain Amyloid Load by Positron Emission Tomography (PET) Imaging	To assess changes in amyloid load over time using Florbetapir ^{8}F (AV-45; Amyvid™) compared to screening (if applicable) and to the start of Part 3. PET scans performed within 12 months prior to the first study drug administration in Part 3 will be used for the baseline of Part 3. This objective will be evaluated in a subset of consenting subjects participating in the PET substudy.
Pharmacokinetics	To determine the relationship of plasma concentrations of gantenerumab on other responses
Anti-Drug Antibodies	To assess the development of anti-gantenerumab antibodies and, if detected, explore their association with the PK, PD, efficacy, and safety parameters of gantenerumab.
Cognition, Global, Functioning, and Dementia Assessment	To evaluate the effect of gantenerumab over time as assessed with the CDR-SOB, the ADAS-Cog, the MMSE, the FCSRT-IR, the CDR global score, the FAQ compared to baseline and to the start of Part 3, and to determine the presence of and time to onset of dementia.
TRIAL DESIGN	Multicenter, randomized, double-blind, placebo-controlled, parallel-group study, followed by open-label extension with active study drug treatment
NUMBER OF SUBJECTS	Approximately a total of 770 subjects; 514 on gantenerumab and 256 on placebo. The sample size was confirmed following a planned blinded evaluation of the variance in the change in the CDR-SOB at Week 76. The study enrolled 799 subjects, and 797 subjects were dosed with double-blind treatment: 266 subjects in the placebo group, 271 subjects in the gantenerumab 105 mg group, and 260 subjects in the gantenerumab 225 mg group. The number of subjects *enrolled in Part 3 is 154*.

TARGET POPULATION	Subjects who meet memory and biomarker criteria which indicate a strong likelihood that they are in the prodromal phase of Alzheimer's Disease
LENGTH OF STUDY	**Double-blind treatment period:** Part 1: Approximately 2 years and 2 months which includes 8 weeks for screening and 2 years (104 weeks) of treatment. Part 2: Up to additional 2 years of treatment. Dosing was suspended on 19 December 2014. As a result duration of the double-blind treatment period varied depending on the number of study weeks that subjects completed. **Treatment-free follow-up period:** Twelve weeks of follow up after completion of the double-blind treatment in Part 1 or Part 2, with an optional follow-up visit approximately 1 year (52 weeks) after the end of the double-blind treatment. Approximate duration of the study for subjects completing both Part 1 and Part 2 with the maximum 52-week follow-up and not continuing in Part 3 will be 5 years and 2 months. For the last subjects enrolled, approximate duration of the study will be 2 years and 2 months (year 1 of Part 1 and 1 year of treatment-free follow-up). **Open-label extension** Part 3: Up to 3 years of active study drug treatment (with a 4-week follow-up visit) after treatment-free follow-up period. For subjects continuing in Part 3, treatment-free follow-up period will last approximately between 12 and 18 months (depending on the approval of study protocol WN25203G by local Competent Authorities). *All subjects who complete 3 years of open-label treatment will be given the option of extending open-label treatment until July 2020 and may receive up to 21 additional administrations every 4 weeks during Years 4 and 5.*
END OF STUDY	The end of the study will be considered to be the date of the last visit (including the last scheduled follow-up visit according to study protocol) of the last subject in the study.
INVESTIGATIONAL MEDICAL PRODUCT(S) DOSE/ROUTE/REGIMEN	Part 1 and Part 2: Gantenerumab (105 or 225 mg for the 0ε4 and 1ε4 ApoE genotypes or 105 mg for the 2ε4 ApoE genotype subjects) by SC injection Q4W Part 3 (open-label extension): Gantenerumab will be administered SC Q4W to the subjects using up-titration regimens dependent on APOE ε4 genotype (and on the dose received during the double-blind treatment period) that will allow subjects to reach the target dose of 1200 mg gantenerumab within 10 and 6 months for titration schedules below. Titration schedule 1: Dosing in APOE ε4 carriers (1ε4 ApoE and 2ε4 ApoE genotypes who were in the placebo and 105 mg gantenerumab groups, and in the 225 mg gantenerumab group meeting criteria for dose reduction due to amyloid-related imaging abnormalities (ARIAs) during double-blind treatment period): • Doses 1, 2, and 3: 105 mg • Doses 4, 5, and 6: 225 mg • Doses 7 and 8: 450 mg • Doses 9 and 10: 900 mg • Dose 11 onwards: 1200 mg

	Titration schedule 2: Dosing in subjects who are APOE ε4 non-carriers (0ε4 genotype) and in APOE ε4 carriers receiving 225 mg gantenerumab until the end of double-blind treatment (1ε4 genotype): • Doses 1 and 2: 225 mg • Doses 3 and 4: 450 mg • Doses 5 and 6: 900 mg • Dose 7 onwards: 1200 mg Gantenerumab doses of 105 and 225 mg will be administered SC [redacted] The 1200-mg gantenerumab dose will be administered SC [redacted].
COMPARATOR DOSE/ROUTE/REGIMEN	Placebo, by SC injection, Q4W in Part 1 and Part 2.
PART 3 ASSESSMENTS OF:	
- EFFICACY	CDR-SOB, ADAS-Cog, MMSE, FAQ, FCSRT-IR, CDR global, onset of dementia*, during the initial 3 years of Part 3. After which only MMSE will be administered.*
- SAFETY	MRI, physical and neurological examinations, vital signs, laboratory assessments (blood safety tests, urine pregnancy [for women of childbearing potential]), Columbia-Suicide Severity Rating Scale (C-SSRS), ECGs, and adverse event monitoring
- PHARMACOKINETICS	Gantenerumab levels in plasma
- BIOMARKERS	MRI and PET, to assess changes in brain volumetry and brain amyloid load over time *during the initial 3 years of Part 3*, respectively.

PROCEDURES (summary):

Screening and baseline: After written informed consent is obtained, screening assessments, which include general health and cognitive testing, brain MRI, and lumbar puncture for cerebrospinal fluid (CSF) collection, and must be completed within 8 weeks followed by up to 1 week for baseline assessments. (See schedule of assessments in protocol)

Treatment (Part 1): In this study, all subjects will receive 26 treatments (drug administrations) with a 4-week interval between each dose. On each dosing day, gantenerumab or matching placebo will be administered as two SC injections in the abdominal area. Safety and efficacy evaluations will be performed according to the schedule of assessments.

Treatment Extension (Part 2): Subjects who complete the entire 2 years of treatment and the Week 104 follow-up visit may continue to receive the same treatment that they were receiving at the Week 100 visit. The double-blind treatment can resume at the Week 104 visit after all assessments have been completed for that visit.

Follow-up: Subjects will be followed for 12 weeks, with an optional follow-up visit approximately 1 year (52 weeks) after the last dose of study treatment in Part 1 or Part 2 (double-blind treatment phase). The Week 52 visit is not required for subjects entering Part 3.

Futility Analysis: A futility interim analysis was performed when approximately 50% of the sample size completed the Week 104 visit. As the study was declared futile, with a low likelihood of meeting the prespecified primary outcome measure with the doses studied (105 and 225 mg), dosing was suspended on 19 December 2014. This analysis did not reveal any new safety signal.

Open-Label Extension (Part 3): Additional analyses of efficacy and PD results (CSF biomarkers of neurodegeneration and amyloid PET standardized uptake value ratio [SUVR]) indicated that higher doses of gantenerumab may have clinically relevant effect on cognition and function. Doses were modeled based on the results of the PET substudy (brain amyloid PET SUVR) and on the supportive results of the Phase 1b (PRIME) study, investigating the effects of aducanumab on a total of 165 patients with prodromal or mild AD. Aducanumab is a monoclonal antibody with similar properties and mode of action as gantenerumab. The results showed a dose- and time-dependent reduction of amyloid plaques in the brain that was associated with dose-dependent clinical effect, which reached statistical significant clinical effect with the highest aducanumab dose tested. Extrapolation of the data indicated that approximately 20% reduction in brain amyloid detected by PET may be needed to achieve clinical effect, compared to overall approximately 5% achieved with 225 mg gantenerumab over 2 years.

All subjects who were eligible for and enrolled into protocol WN25203 and had at least one follow-up/dropout visit after the double-blind treatment will be offered the opportunity to participate in Part 3. Subjects who meet any of the following criteria will be exempted:

- Prematurely discontinued from Part 1 and Part 2 for safety reasons (e.g., MRI findings meeting criteria for treatment discontinuation in Part 1 and Part 2)
- [redacted]
- Received another investigational medication after the end of double-blind treatment
- Participation in Part 3 deemed inappropriate by investigator or Sponsor

During Part 3 study, subjects will receive gantenerumab Q4W that will be uptitrated starting from 105 or 225 mg based on the ApoE genotype to up to 1200 mg to reach the doses expected to give clinically meaningful effect in a less than 1 year. The titration schemes were designed to optimally manage ARIA events in ApoE e4 carriers and non-carriers by a PK-PD model using PK and safety results from this study and from similarly acting anti-amyloid antibodies (aducanumab and bapineuzumab). In addition, all subjects entering Part 3 at centers already involved in a WN25203 PET substudy of brain amyloid imaging during Part 1 and Part 2 will be offered to take part in the PET substudy, independent of their previous participation during the double-blind treatment. Subjects will be followed until the end of treatment phase (4 weeks after the last dose).

STATISTICAL ANALYSES IN THE OPEN-LABEL EXTENSION:

Statistical analyses will primarily focus on safety aspects during and after the uptitration phase in Part 3 of the trial. In addition, it is planned that efficacy analyses will be conducted on cognitive and functional measures as well as biomarkers. It is planned that efficacies will be calculated using both, the original, drug-naïve baseline as well as the baseline that gets available before start of *Part* 3. Results of these analyses will be interpreted in an exploratory fashion.

GLOSSARY OF ABBREVIATIONS

Aβ	Amyloid-beta
AChEI(s)	Acetylcholinesterase Inhibitor(s)
AD	Alzheimer's disease
ADA	Anti-drug antibodies
ADAS-Cog	Alzheimer Disease Assessment Scale-Cognition
ADL	Activities of Daily Living
ADNI	Alzheimer's Disease Neuroimaging Initiative
AE	adverse event
ApoE	gene encoding Apolipoprotein E
ARIA	Amyloid Related Imaging Abnormality
ARIA-E	Amyloid Related Imaging Abnormality-Edema
ARIA-H	Amyloid Related Imaging Abnormality-Hemosiderin
AUC	area under the plasma concentration-time curve
$AUC_{0-\tau}$	area under the time-plasma concentration curve at steady state
AUCinf	area under the plasma concentration-time curve from time zero extrapolated to the infinite time
CA	Competent Authorities
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDR	Clinical Dementia Rating Scale
CDR-SOB	Clinical Dementia Rating – Sum of Boxes
Cmax	maximum plasma concentration
Cmin	minimum plasma concentration
CSF	cerebrospinal fluid
CSR	Clinical Study Report
C-SSRS	Columbia-Suicide Severity Rating Scale
Ctrough	trough concentrations
CV	coefficient of variation
DMS	Delayed match to sample
DO	dropout

GLOSSARY OF ABBREVIATIONS

DSM	Diagnostic and Statistical Manual of Mental Disorders
EC	Ethics Committee
eCRF	Electronic Case Report Form
EDC	electronic data capture
EEA	European Economic Area
ELISA	Enzyme Linked Immunosorbent Assay
Ext	extension
FAQ	Functional Activities Questionnaire
FCSRT-IR	Free and Cued Selective Reminding Test – Immediate Recall
FcγR	Fragment crystalizable gamma Receptor
FDA	U.S. Food and Drug Administration
FLAIR	Fluid-attenuated Inversion Recovery
FU	follow-up
GDS	Geriatric Depression Scale
HAHA	Human-antihuman antibodies
HbA1c	Hemoglobin A1c (glycosylated hemoglobin)
HCLF	high concentration liquid formulation
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
iDMC	Independent Data Monitoring Committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
IgG	Immunoglobulin G
IMC	*internal monitoring committee*
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INN	International Non-proprietary Name
ITT	intent to treat
IV	intravenous

GLOSSARY OF ABBREVIATIONS

IVRS	Interactive Voice Recognition System
IxRS	Interactive Voice Recognition System or Interactive Web Recognition System
Kd	dissociation constant
LOCF	Last observation carried forward
LP	Lumbar puncture
[redacted]	[redacted]
MAD	Multiple Ascending Dose
MCI	Mild Cognitive Impairment
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
MMRM	Mixed-effects model repeated measures
MMSE	Mini Mental State Exam
MOT	Motor screening test
MRI	Magnetic resonance imaging
MRI-C	MRI Review Committee
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	*open-label extension*
PAL	Paired associates learning
PD	Pharmacodynamic
PET	Positron Emission Tomography
[redacted]	[redacted]
PK	Pharmacokinetic
PP	per protocol
PRM	Pattern recognition memory
PT	Prothrombin time
P-tau	phospho-tau

GLOSSARY OF ABBREVIATIONS

Q4W	every 4 weeks
QC	quality control
QTcF	QT corrected with Fridericia equation
RCR	Roche Clinical Repository
RTI	Reaction time
RVP	Rapid visual information processing
SAD	Single ascending dose
SAE	serious adverse event
SC	subcutaneous
SD	Standard deviation
SEAG	Science and Ethics Advisory Group
SMT	Study Management Team
SNRI	Selective Norepinephrine Reuptake Inhibitor
SSNRI	Selective Serotonin/Norepinephrine Reuptake Inhibitor
SUVR	Standardized Uptake Value Ratio
SSRI	Selective Serotonin Reuptake Inhibitor
SUSAR	Suspected Unexpected Serious Adverse Reaction
SWM	Spatial working memory
T	Tesla
T4	thyroxine
Tmax	maximum plasma concentration
T-tau	total tau
ULN	upper limit of normal

PART I: STUDY DESIGN AND CONDUCT

1. BACKGROUND AND RATIONALE

1.1 Background (Additional Information May Be Found in the Investigator's Brochure)

1.1.1 Alzheimer's Disease

According to the figures provided by Alzheimer's Association in 2015, an estimated 47 million people are living with dementia, with the number projected to increase to 76 million cases in 2030. Alzheimer's disease (AD) is the most common cause of dementia, accounting for 60%–80% of cases. In the United States it is the sixth leading cause of death, with the rate increased by 71% from 2000 to 2013.

AD is clinically characterized by a progressive impairment in cognitive and executive abilities, which results in decreased function and gradual loss of independence [39]. Although the course of illness will vary from patient to patient, in general, the clinical picture evolves from "predementia/prodromal AD" to mild, moderate, and ultimately, severe AD. The progressive decline that starts in the predementia stage of AD initially presents as an impairment of memory, language, and visuospatial function, some of which can be explained by loss of cholinergic neurons in the basal forebrain. This neuronal loss contributes to the symptom development of AD. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. Because of its increasing prevalence, long duration, and high cost of care, AD is expected to continue to represent a major public health problem.

The main pharmacological approach to treatment is aimed at ameliorating the symptoms and improving functioning of AD patients for 6–18 months by increasing synaptic levels of acetylcholine through the use of acetylcholinesterase inhibitors (AChEIs). Currently available AChEIs include donepezil (Aricept®), galantamine (Reminyl®/Razadyne®), rivastigmine (Exelon®), and tacrine (Cognex®) [40]. Overstimulation of the N-methyl-D-aspartate (NMDA) receptor by glutamate is also implicated in neurodegenerative disorders [40]. Memantine, an NMDA antagonist, provides only modest improvement in global measures of functioning both with and without an AChEI. Unfortunately, none of these medications have an effect on the progressing neuropathology nor significantly change the course of the disease [40].

Consequently, drug discovery and development in AD are focused on disease-modifying treatments that target, for example, amyloid-beta (Aβ) peptide or tau pathology. Genetic and pathological evidence suggests that Aβ processing and deposition play a critical role in the cascade of biological events involved in the pathogenesis of AD. Aβ accumulation in the brain begins well before the development of clinical dementia in AD, and studies have shown that while intermediate or high levels of Aβ may be present at a very early disease stage (previously referred to as amnestic Mild Cognitive Impairment [MCI]), near maximal amounts are generally reached by the time dementia is evident [1]. For these reasons, treatments which prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD. Accumulating evidence suggests that monoclonal anti-Aβ antibodies can bind to Aβ and promote its clearance [16,41,42], thus

potentially reducing deposition of Aβ aggregates, reducing neurodegeneration, and, ultimately, slowing progression of AD.

1.1.2 Gantenerumab

Gantenerumab or RO4909832 is a fully human anti-Aβ peptide antibody developed by in vitro maturation within a complete human immunoglobulin γ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ demonstrated for both major types of Aβ, i.e., $Aβ_{1-40}$ and $Aβ_{1-42}$. In vitro, gantenerumab recognizes aggregated (fibrillar) Aβ with high affinity (K_d approximately 0.5 nM). Based on further in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans gantenerumab may prevent, inhibit, or reduce the accumulation of Aβ that is believed to play an important role in the pathogenesis of AD.

Gantenerumab was investigated in *10* completed Phase 1 clinical trials: *three* single-ascending-dose (SAD) studies (BN18726*,* JP22474*, and BP30042*)*;* two multiple- ascending-dose (MAD) studies in patients with mild to moderate AD (NN19866 described in Section 1.1.2.1 and JP22431)*;* and *four* bioavailability studies in healthy subjects, one comparing intravenous (IV) and subcutaneous (SC) formulations (WP22461)*,* two comparing lyophilized and liquid SC formulations (WP27951 and BP29113)*, and a relative bioavailability study (WP40052) comparing gantenerumab SC formulation from the G3 manufacturing process (used in the ongoing WN25203 and WN28745 open label studies) to the new G4 manufacturing process, to be used in upcoming studies. In addition, a tolerability study (WP39322) investigating the association of pain with speed of SC administrations of gantenerumab has been completed*. A total of *543* subjects participated in these Phase 1 studies, of whom *406* healthy volunteers and 101 patients with AD received gantenerumab.

Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (the current protocol Study WN25203) and mild AD (Study WN28745) have been converted to open-label extension (OLE) studies. The OLE studies examining the safety and tolerability of higher doses of gantenerumab in prodromal AD (Study WN25203) and in mild AD (Study WN28745) are ongoing. Two additional Phase III studies (WN29922 and WN39658) investigating the effect of gantenerumab in early (prodromal to mild) AD were initiated in 2018.

In addition, a Phase II/III study, the Dominantly-Inherited Alzheimer's Network Trials Unit (DIAN-TU-001), is ongoing.

Information on the preclinical and clinical studies can be found in the Investigator's Brochure (IB) for gantenerumab.

1.1.2.1 NN19866: Clinical Multiple Ascending Dose Study (MAD)

This study was conducted in patients with mild to moderate AD and as mentioned above, a subset of patients had amyloid imaging via *positron emission tomography (*PET*)* scanning. Dosing was an IV infusion given once every 28 days for 7 administrations.

There were four dosing cohorts: the 6 mg and 20 mg cohorts each included 10 patients (8 active, 2 placebo), and the 60 mg and 200 mg cohorts each included 20 patients (16 active, 4 placebo). Due to reports in the literature that other monoclonal antibodies increased cerebral microbleeds in transgenic AD model mice, patients with any microbleeds on the screening magnetic resonance imaging scan (MRI) were excluded.

PET data available from the MAD substudy suggested an amyloid-removing effect of gantenerumab over the period of up to 6 months at doses of 60 and 200 mg IV whereby the effect at the higher dose appeared larger.

Pharmacokinetics showed a terminal half-life of approximately 24 days (similar to other IgG molecules). There was minimal and predictable accumulation in the periphery and CSF concentrations were approximately 0.12%–0.27% of the plasma concentration across the treatment groups.

Monitoring for antidrug antibodies (ADAs) did not reveal an immunogenicity signal.

No changes were seen on measures of cognition or biological fluid markers (in this Phase 1 study with the small sample size and of short duration).

The main clinical safety observations reported were amyloid-related imaging abnormalities (ARIAs). The ARIAs included edema/effusion (ARIA-E) and hemosiderosis (ARIA-H; [microbleeds and areas of leptomeningeal hemosiderosis]) and were also observed with other anti-Aβ therapies (see Section 1.3.3). Standard safety measures (adverse events [AEs], laboratory tests, ECGs, and physical and neurological examinations) demonstrated that all doses were well tolerated.

Six serious adverse events (SAEs) in 6 patients were reported during this study, two of which resulted in death (one case of coronary atherosclerosis in the placebo group and one in the gantenerumab 6 mg group). There were two Suspected Unexpected Serious Adverse Reactions (SUSARs) (i.e., serious adverse events where an association with treatment cannot be excluded): cerebral microbleed and left bundle branch block. Both subjects had received 200 mg of gantenerumab. No patient withdrew prematurely from the study due to an adverse event.

Study NN19866 was prematurely terminated due to MRI findings consistent with ARIA-E (vasogenic oedema/inflammation) seen after two to four doses of gantenerumab 200 mg. Two of the 16 patients in this dose group were homozygous for ApoE4 (ε4/ε4), and each had distinct ARIA-E and ARIA-H; 1 patient also had associated symptoms that were reported as a serious adverse event (cerebral microhemorrhage) but no treatment was required. Of the 11 patients who were heterozygous for ApoE4 (ε4/ε3), two had minor ARIA-E findings. There were no such MRI findings in the 3 patients who were ApoE4 non-carriers. Concomitant ARIA-H (ie, concomitant microbleeds) findings were only seen in the two patients who were homozygous for ApoE4. No patient required treatment, and the ARIA-E findings spontaneously resolved 1-4 months after discontinuation of gantenerumab.

Three patients had isolated microbleeds (without ARIA-E): one placebo patient (ε4/ε3) had two microbleeds, and single microbleeds were seen in 1 patient at 60 mg (ε4/ε4) and

1 patient at 200 mg (a non-ApoE4 carrier). Overall, isolated microbleeds were uncommon and did not show a convincing relationship to treatment.

Because microbleeds are associated with increased cerebrovascular amyloid and this may increase the risk for an MRI finding, including further hemorrhages when treated with an anti-Aβ antibody, Study WN25203 restricts patient enrollment based on the number of microbleeds seen on the screening MRI. In addition, the protocol includes an algorithm for adjusting treatment should ARIA-H or ARIA-E finding described above occur. Subjects will be monitored by regularly scheduled MRIs which will be centrally read and any relevant new findings will be brought to the attention of an independent MRI Review Committee (MRI-C) (see Section 5.1.3.1).

1.1.2.2 Clinical Pharmacokinetics following Subcutaneous Dosing

The pharmacokinetics of gantenerumab following a single SC dose [redacted] in healthy subjects were compared with IV administration (Study WP22461) and with SC administration of the high concentration liquid formulation (HCLF; Studies WP27951 and BP29113).

Absorption of gantenerumab is relatively slow after SC injection, with plasma concentrations reaching maximum levels generally 7 days after dosing, followed by a subsequent monophasic decline with a terminal half-life of approximately 24 days, and is similar to that recorded following IV administration. [redacted]

SC administration of gantenerumab caused minimal local erythema and transient pain. In Study WP27951, the most common adverse event was injection site erythema, [redacted]. It is likely that the injection site reactions may be at least partly related to the injection volume. See the IB for additional information.

1.1.2.3 WN25203

The study enrolled 799 subjects and 797 subjects were dosed with double-blind treatment: 266 subjects in the placebo group, 271 subjects in the gantenerumab 105 mg

group and 260 subjects in the gantenerumab 225 mg group. One hundred twelve subjects participated in the PET substudy.

Randomization was based on the ApoE ε4 carrier status (Section 1.3.3). In the context of the clinical understanding of ARIAs at the time of study design, selection of gantenerumab doses (105 mg for 2ε4 genotype and 225 mg for 0ε4- and 1ε4 genotype) was largely driven by reducing risk of MRI findings. Baseline characteristics were well balanced between treatment arms in the study, as well as in the PET substudy. Per protocol, subjects were to be treated for 2 years (104 weeks) with an option for additional 2 years of double-blind treatment.

Unblinded safety data were reviewed on an ongoing quarterly basis by the independent Data Monitoring Committee (iDMC). A planned interim futility analysis was performed by the iDMC when approximately 50% of the sample completed 104 weeks of treatment (see Section 10.2.3). Following the analysis that estimated a low probability for meeting the pre-specified primary outcome measure (with the predictive probability of success of 6%), the study was declared futile. As a result, dosing with originally selected doses (105 mg and 225 mg) was suspended on 19 December 2014.

This analysis did not reveal any new safety signals. Approximately 90% of the patients experienced at least one AE, with the incidence comparable between the treatment arms. Incidence of SAEs was 19.5%, 17.3%, and 16.9% in the placebo-, gantenerumab 105 mg- and gantenerumab 225 mg groups, respectively. ARIAs and injection-site reactions remain the main clinical safety findings for gantenerumab. Comprehensive information on ARIA events in the study is provided in Section 1.3.3. Regarding injection site reactions, overall incidence in the study in the safety population (797 subjects) was 15.4% with majority of the events of mild intensity. Incidence of injection site reactions by treatment arm was 4.5%, 18.8%, and 23.1% in the placebo-, gantenerumab 105 mg- and gantenerumab 225 mg groups, respectively, leading to withdrawal in only 2 cases. Notably, there was no difference in overall withdrawal rate between the treatment arms. The number of subjects withdrawing because of adverse event (which includes withdrawals due to protocol-imposed measures mandating treatment discontinuation as part of management of MRI findings) was 14 (5.3%), 23 (8.5%) and 25 (9.6%) subjects in the placebo-, gantenerumab 105 mg- and gantenerumab 225 mg groups, respectively. Overall, gantenerumab doses studied in the double-blind phase of Study WN25203 were safe and well tolerated [49].

Additional analyses indicated that higher doses of gantenerumab may have clinically relevant effects on cognition and function, prompting the Sponsor to provide subjects the opportunity to be treated with higher doses of gantenerumab in an open-label extension (including those who were in the placebo group), as outlined in Sections 1.2.3 (Rationale for the Open-Label Extension) and 1.3.2 (Reduction in Brain Aβ by Gantenerumab), with dosing regimen designed to minimize the risk of ARIAs (Section 1.3.3). [redacted]

1.1.2.4 WN28745

Study WN28745 was designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were up-titrated independent of their APOE ε4 genotype, starting at 105 mg of SC gantenerumab every 4 weeks (Q4W) for the first 24 weeks, with a subsequent dose increase to 225 mg, based on acceptable MRI scan results. The study enrolled 389 patients, and 387 patients were treated. Following the futility analysis (see Section 1.1.2.3) in this study (WN25203), recruitment was stopped but double-blind dosing continued. In a PET substudy of brain amyloid imaging (WN28745-PET), 108 patients were enrolled. The study was converted to an OLE study evaluating the safety and tolerability of gantenerumab doses up to 1200 mg.

1.1.2.5 WN25203 and WN28745 Open-Label Extension Studies

As of 13 February 2018, 384 patients had been enrolled in the OLE studies WN25203 (154 patients) and WN28745 (230 patients), with 365 patients exposed to gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in the double-blind parts of these studies), and 289 patients have reached the OLE target 1200-mg dose. Safety data and MRI findings are continuously monitored by an internal monitoring committee (IMC). The iDMC was also reviewing relevant safety findings from both OLE studies on a regular basis until the majority of patients have reached the target dose and no new safety signal has been identified in these ongoing studies. The last meeting took place on 10 April 2017; the iDMC reviewed the data with the cutoff date of 13 February 2018 and recommended to continue both OLE studies without modification. All relevant new MRI findings are brought to the attention of the MRI-C, as described in Section 5.1.6.1. The safety profile of gantenerumab when administered at doses up to and including 1200 mg remains comparable to the safety profile of gantenerumab at lower doses (investigated during double-blind Studies WN25203 and WN28745), with injection-site reactions and ARIAs remaining the only identified risks for gantenerumab.

From the open-label studies WN25203 and W28745, 81 patients continued in the respective amyloid-PET substudies of brain amyloid imaging using Florbetapir ^{18}F (Amyvid™). As of 31 August 2017, 40 patients treated with 900–1200 mg gantenerumab for ≥6 months across both open-label studies had a scheduled PET scan at OLE Week 52 (see Section 1.3.2 for results).

1.2 Rationale for the Study

1.2.1 Rationale for Part 1 of the Study

As described above, the accumulation of Aβ generally begins well before the onset of AD dementia and probably even before any cognitive decline associated with AD. It is therefore reasonable to think that the benefit of anti-amyloid therapy may be greater if initiated before prominent symptoms of AD manifest, such as dementia. Consistent with

this concept, this study will enroll subjects who do not yet meet a diagnosis for Alzheimer's dementia but have findings that characterize the predementia or prodromal phase of AD [3]. The main selection criteria used here for prodromal AD are: a report of a recent gradual decline in memory function, impaired episodic memory on testing, a Clinical Dementia Rating scale (CDR) global score of 0.5, a CDR memory score of 0.5 or 1 and a CSF $A\beta_{1-42}$ level of less than 600 pg/mL [as measured by Innogenetics Enzyme Linked Immunosorbent Assay (ELISA) assay at a central testing laboratory; the threshold is based on extensive literature derived from multicenter studies in the US and Europe, and data available at the central laboratory]. In addition the subject cannot meet criteria for dementia and there can be no other better explanation for the findings than prodromal AD.

Many of the selection criteria for this study are based on the selection criteria for amnestic MCI subjects in the Alzheimer's Disease Neuroimaging Initiative (ADNI) protocol [4]. The ADNI study itself based its selection criteria on the Alzheimer's Disease Cooperative MCI Study of vitamin E and donepezil [5]. In both studies MCI subjects converted to Alzheimer's dementia at a rate of approximately 16% per year with few subjects reverting to normal cognition or developing a dementia that was not of the Alzheimer's type. The main difference in the selection criteria for this study is the requirement for a low CSF $A\beta_{1-42}$ level.

Alzheimer's disease is characterized by changes in CSF biomarkers which reflect the disease pathology. The AD biomarker signature consists of reduced CSF $A\beta_{1-42}$, a marker of amyloid deposition, and elevated total tau (T-tau) and phospho-tau (P-tau), which reflect neurodegeneration [6]. Studies, including several large multicenter ones, have consistently shown that these biomarkers have a high predictive value for identifying prodromal AD in patients with MCI; estimates for sensitivity and specificity vary in these studies due to different factors including the combination of biomarkers, patient follow up time, and inter-site assay variability [7, 8, 9]. Within ADNI, CSF $A\beta_{1-42}$ was identified as the most sensitive marker for AD detection using an independent autopsy confirmed AD cohort (96.4% sensitivity, 95.2% negative predictive value, 78.6% specificity, and 81.8% positive predictive value) [9]. When a cutoff for this marker defined in the above autopsy cohort was applied to MCI patients, an incidence of an AD-like profile of 86.5% was reported for the relatively small number of MCI patients who converted to dementia of the AD type within a year of the study start; in contrast the incidence of this biomarker profile was 74% in all MCI patients [9]. Even though future work will be needed to further characterize the utility of the above CSF biomarkers, the accumulated body of evidence from multiple studies indicates that they can be used in clinical trials to enrich MCI populations with AD patients. The fact that gantenerumab is an anti-amyloid agent is an additional reason to select patients based on low CSF $A\beta_{1-42}$ in this study. As indicated above, selecting MCI subjects who have low CSF $A\beta_{1-42}$ will increase the likelihood that they are actually in the early stages of Alzheimer's disease and therefore will likely show cognitive decline/progress clinically during the study. Due to the rigorous screening procedures in this study including centralized MRI reading and CSF biomarkers assessment, and specifically selected cognitive testing, it is expected that relatively few cases of non-AD patients will be enrolled. The amyloid based enrichment criterion allows the study objective to be answered with relatively fewer subjects and

increase the possibility to observe an effect from the therapy. As anti-amyloid therapy is not expected to provide any acute symptomatic improvement, a 2–year treatment period was selected.

In addition, in certain centers consenting subjects will participate in a substudy of PET brain amyloid imaging in an attempt to assess whether gantenerumab, at the doses selected, can remove fibrillar brain amyloid as determined by amyloid PET. Details of this substudy are described in a separate protocol.

1.2.2 Rationale for Part 2 of the Study

Subjects who completed Part 1 of the study through the Week 104 visit could enter the optional extension part of the study and continue receiving the same treatment for up to 2 additional years. The rationale for Part 2 is to assess the long-term safety of gantenerumab as well as effects on biomarkers after an additional 2 years of treatment (e.g., PET, brain volumes, CSF markers).

Continuing the placebo control is important for discerning effects due to gantenerumab from those due to advanced age, more advanced cognitive impairment, and concurrent illness. Analyses of cognition and functioning assessed in Part 2 will be exploratory, due to the high rate of attrition expected in a study in this population and of this duration. During Part 2, approved symptomatic treatments for AD are permitted at the discretion of the Principal Investigator. Dosing in Parts 1 and 2 of the study was terminated on 19 December 2014 as a result of the planned futility analysis, and subjects continued with treatment-free safety follow-up as per protocol.

1.2.3 Rationale for the Open-Label Extension (Part 3)

The futility analysis revealed low likelihood for trial success with the original doses studied. The decline in the primary endpoint, Clinical Dementia Rating – Sum of Boxes (CDR-SOB) scale observed across treatment groups over 2 years was approximately 1.06 (lower than expected for this population, see below). No significant differences were detected between treatment arms over 2 years in the secondary endpoints, Mini Mental State Exam (MMSE), Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog)-13 or Functional Activities Questionnaire (FAQ). In addition, no significant differences were observed across groups on any cognitive or functional measure by pre-specified mixed model repeated measures analysis (MMRM; Section 8.2.1). Furthermore, subgroup analysis, based on larger number of baseline characteristics (demographics, cognitive, CSF biomarkers, and disease severity) or ApoE ε4 allele status, did not reveal any differences compared to the overall population.

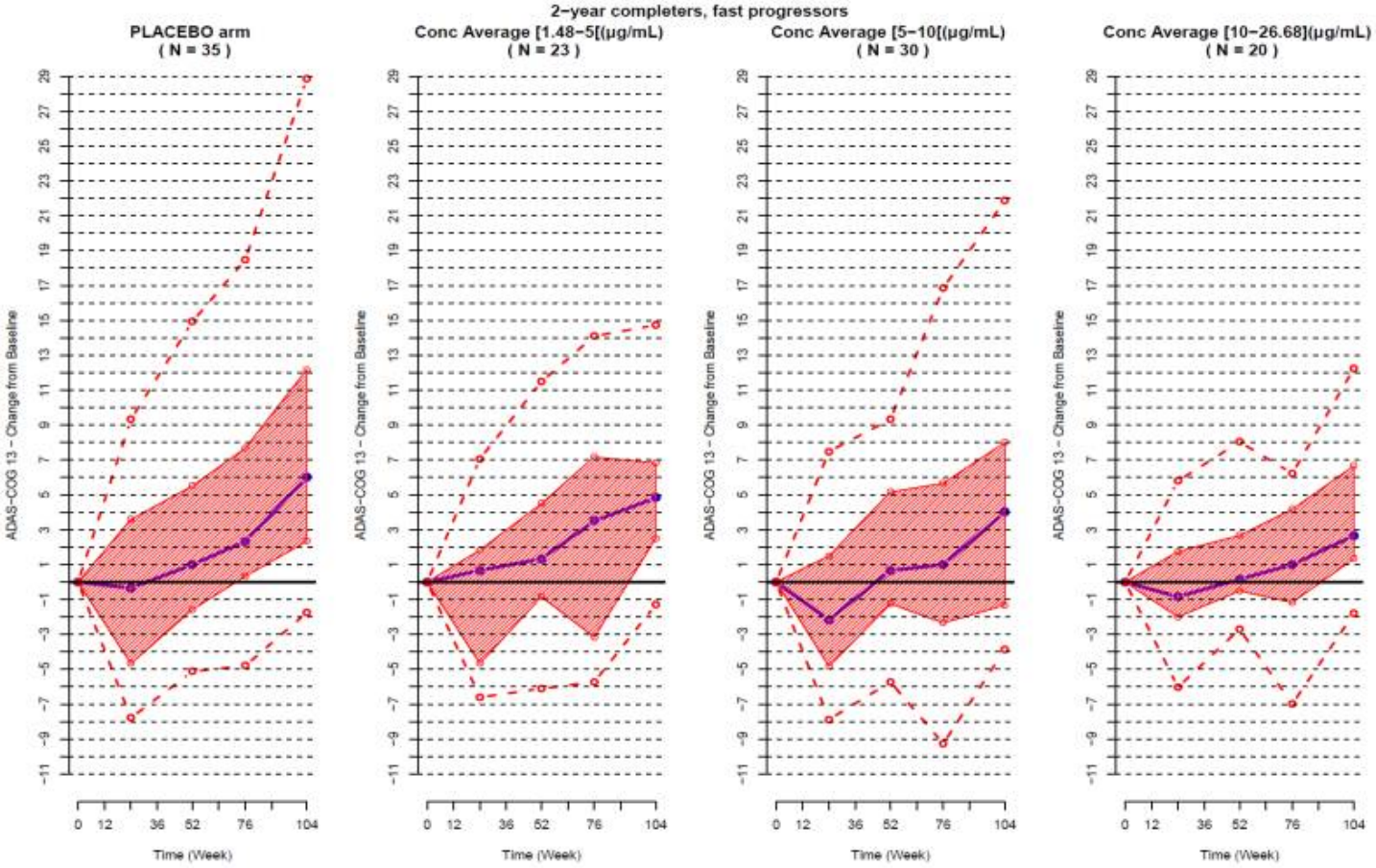
Additional analyses indicated that the rate of clinical decline was lower than predicted for this study population (with higher than expected proportion of “slow-progressors”) and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were sub-therapeutic and that a higher gantenerumab dose should have clinically relevant effect [49]:

1. Study WN25203 was the first global study in prodromal AD to use amyloid screening to enrich the patient population and create a more homogenous prodromal AD population, which was predicted to decline by approximately 1.92 points in CDR-SOB

over the course of the 2-year study, compared with the observed decline of 1.06 points. Based on an independent ADNI-based model that identified "fast progressors" by baseline characteristics [43], only one-third of the studied population would be in this category, whereas the majority did not have anticipated clinical decline over the 2-year period. Among "slow progressors", clinical decline was similar across treatment groups (3-point change in ADAS-Cog-13). In contrast, among "fast progressors", there was a clear differentiation dependent on gantenerumab exposure, with a 6-point increase in the placebo group compared to a 3-point increase in the group with the highest gantenerumab concentration (Figure 1). Similar drug concentration-dependent trends were observed for MMSE and Cambridge Neuropsychological Test Automated Battery (CANTAB) results, although no trend could be observed for CDR-SOB.

2. Significant treatment effect could be detected by posthoc multi-filter analysis in a subject subpopulation with a more pronounced pathology at baseline (CDR-SOB ≥ 2, FAQ ≥ 4, and hippocampal volume less than median), a p-value <0.05 on ADAS-Cog-13, and a CANTAB with 225 mg gantenerumab dose. The limitation of this analysis is a relatively small sample size with approximately one quarter of the enrolled prodromal study population.
3. Dose-dependent changes were observed after 2 years of treatment for the biomarkers of neurodegeneration assessed in the cerebrospinal fluid (CSF), P-tau and T-tau. Reduction of P-tau reached significance with 225 mg gantenerumab versus placebo ($p<0.01$). Mean percent changes for P-tau were 2.62, −4.85, −7.52, for placebo, 125 mg and 225 mg gantenerumab groups, respectively (Figure 2A), and for T-tau 3.11, −1.45 and −2.94 (Figure 2B).
4. Decrease in amyloid load was detected in PET substudy with 225 mg gantenerumab. After 2 years of treatment, mean percent change from baseline in amyloid PET Standardized Uptake Value Ratio (SUVR) using the cerebellum was −1.11, 0.19, and −5.37 in the placebo-, gantenerumab 105 mg and gantenerumab 225 mg group, respectively. Details are provided in Section 1.3.2 (Reduction in Brain Aβ by Gantenerumab).

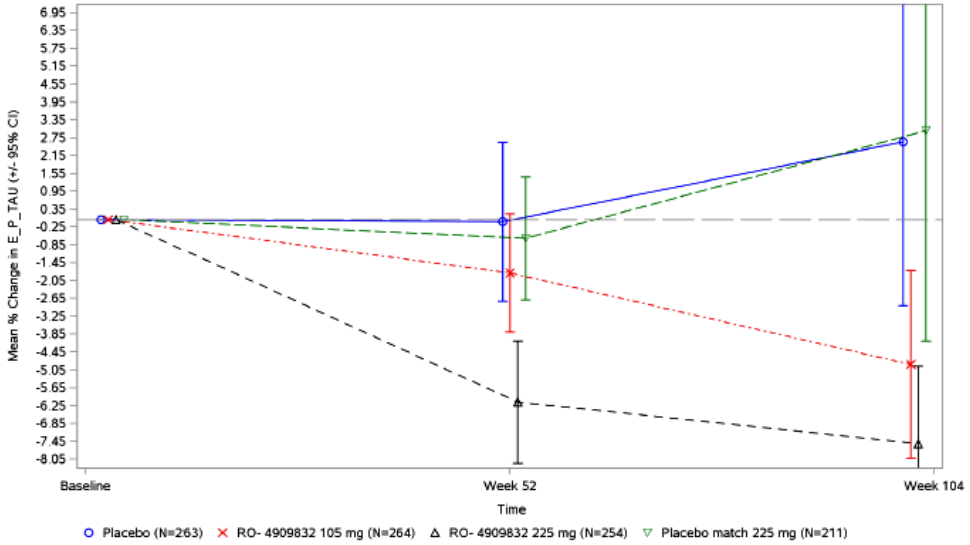
Figure 1 **Treatment Response in ADAS-Cog-13 by Gantenerumab Serum Concentration, 2-Year Completing Fast Progressors**



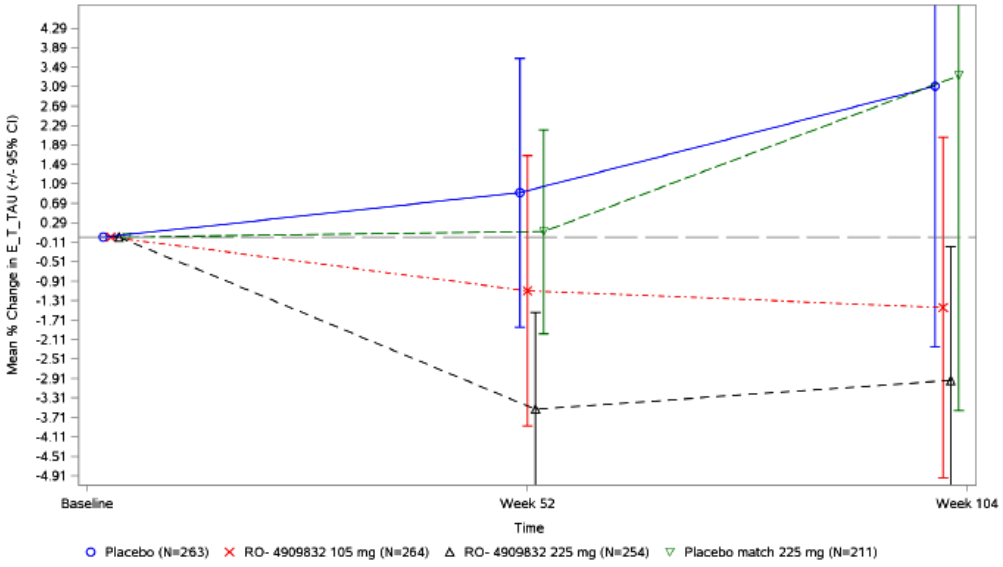
Purple bold line = ≤ median; shaded = 50% observations; red dotted line = 5th and 95th percentile

Figure 2 **Mean Percent Changes from Baseline after 2 Years of Treatment in (A) CSF P-Tau and (B) T-Tau (ITT population)**

A



B



Further supportive data came from the results of Phase 1b trial (PRIME; NCT01677572), which examined effects of an anti-Aβ monoclonal antibody, aducanumab (Biogen) versus placebo (1, 3, 6, and 10 mg/kg by IV infusion every 4 weeks [Q4W]), in 165 prodromal and mild AD patients. Aducanumab and gantenerumab display a number of similar biological, PK and pharmacodynamic (PD) features. Both are fully human antibodies of IgG1 isotype that recognize a conformational epitope at the N-terminus of Aβ, binding preferentially to the Aβ aggregates with a similar affinity, have a similar brain penetration and exert their action by microglia-mediated clearance of amyloid

plaques. PRIME results showed a significant dose- and time-dependent reduction of brain Aβ plaques versus placebo by PET imaging that was associated with dose-dependent slowing of decline on MMSE and CDR-SOB observed at 1 year, which reached statistical significance with the highest aducanumab dose. PET SUVR showed no changes or very minimal changes at Weeks 26 and 54 in the placebo and 1 mg/kg treatment arms, respectively; whereas, statistically significant reductions were observed in the higher doses. Aducanumab had an acceptable safety profile at Week 54, the main findings being ARIA-E*s* that were dose- and APOE ε4 status dependent.

Considering the similar properties of gantenerumab and aducanumab, PK-PD models *were* developed based on PK, PD, efficacy, and safety results from WN25023 and PRIME studies, allowing prediction of clinically effective dose and dosing regimen to leverage safety. All subjects who were eligible for and enrolled in Study WN25203 and had at least one follow-up/drop-out visit after double-blind treatment will be offered the opportunity to receive active treatment with higher gantenerumab doses (predicted to have relevant clinical effect) in *an* open-label extension, Part 3*, initially for 3 years* (unless exempted for the reasons listed in Section 4.4). In addition, all subjects entering Part 3 at centers already involved in a WN25203 PET substudy of brain amyloid imaging will be offered to take part in the PET substudy, independent of their previous participation during double-blind treatment. To ensure the minimum number of participants in the PET substudy during Part 3, additional centers may be included. A PET scan previously done for the Study WN25203 within 12 months prior to first dose in Part 3 does not need to be repeated.

During Part 3, approved symptomatic treatments for AD will be permitted at the discretion of the Principal Investigator.

1.2.4 Rationale for Prolonging Open-Label Extension (Part 3)

As of 13 February 2018, a total of 384 patients have been enrolled in the OLE studies (WN25203 and WN28745) with no new identified safety findings. Because AD is characterized by progressive decline, it will be important to further characterize the long-term safety of gantenerumab beyond the initial 3 years. Given that the safety profile of gantenerumab in the OLE studies remains similar compared with the double-blind studies, the duration of both OLE studies will be increased. Treatment duration in Part 3 of this study (WN25203) will be extended until the end of July 2020, at which time anticipated results from other relevant monoclonal antibody treatments will be available. The Sponsor will then evaluate the appropriateness of providing patients continued gantenerumab anti-amyloid treatment.

1.3 Overall Benefit-Risk Assessment

As described in Section 1.1.1, one of the leading explanations for the cause of AD is the accumulation of Aβ in the brain. In addition it has been shown that by the time a diagnosis of AD can be made due to the development of dementia, brain Aβ has already reached maximal or near maximal amounts [*10,* 11, 12]. It has therefore been hypothesized that treatments directed at reducing Aβ may be more effective, or perhaps may only be effective, if begun early in the course of AD and specifically before the

onset of dementia. As such, the purpose of this study is to determine whether gantenerumab, which has been shown to reduce brain Aβ in AD patients by PET scan, can benefit subjects when treatment is initiated in the pre-dementia or prodromal stage of AD.

Section 1.3.1 describes how it is now possible to make a reliable diagnosis of prodromal AD by using the recent advances in knowledge and laboratory techniques regarding biomarkers in AD.

Section 1.3.2, describes the reduction in brain amyloid with gantenerumab, which hopefully will be the underlying basis for any benefit of gantenerumab.

Finally in Section 1.3.3 the various measures taken throughout the protocol to minimize risks of MRI events are discussed.

The benefit-risk for Part 2 (the optional extension) is in Section 1.3.6.

Section 1.3.7 depicts the benefit-risk for the open-label extension (Part 3).

1.3.1 Selecting Prodromal AD Subjects for Study WN25203

The selection criteria for Study WN25203 are designed to select subjects with prodromal or pre-dementia AD, which are MCI subjects who have a very high likelihood of having AD pathology. The ability to accurately identify such subjects has been made possible by advances in AD biomarkers. Consensus is developing in the field about how these individuals can be identified. A group of internationally renowned experts proposed an updated diagnostic criteria for (a) AD dementia, (b) MCI due to AD, and (c) for preclinical AD [34]. The criteria for MCI due to AD contains a description of "prodromal Alzheimer's Dementia" which requires the kind of cognitive decline specified in this study as well as a positive biomarker for the molecular neuropathology of AD such as low CSF $A\beta_{1\text{-}42}$. These criteria were based on studies such as the one by Hansson et al. [8] where individuals with MCI (and controls) were followed for 4–6 years. CSF biomarkers assessed at baseline (see Figure 3 below) show low CSF $A\beta_{1\text{-}42}$ in MCI subjects who convert to clinical AD dementia (MCI-AD) as opposed to MCI patients who progress to a different type of dementia (MCI-Other), or remain stable over the course of the observation (Stable MCI).

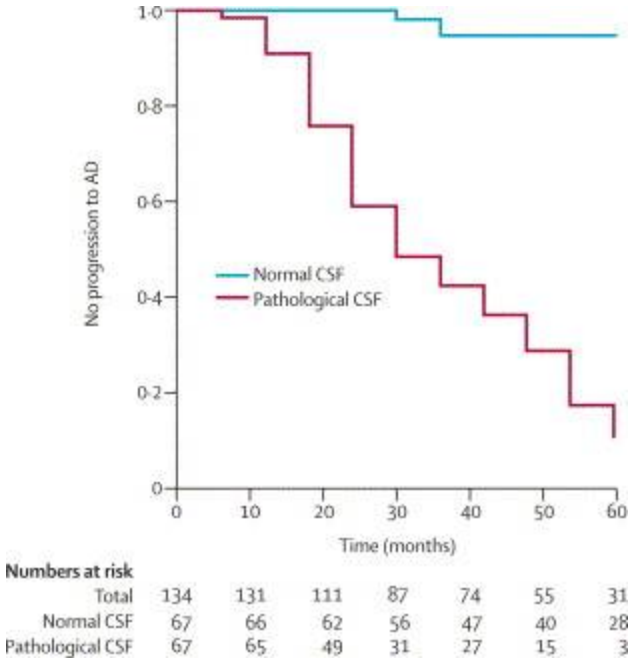
Figure 3 CSF Biomarkers at baseline in MCI subjects (taken from [8])

	N	T-tau (ng/L)	P-tau$_{181}$ (ng/L)	Aβ42 (ng/L)	Aβ42/P-tau$_{181}$ ratio
Controls	39	326 (157)	61 (17)	700 (181)	12·5 (4·7)
Stable MCI	56	340 (212)	62 (16)	551 (188)*	9·5 (3·8)*
MCI-AD	57	816 (426)*†	95 (29)*†	324 (101)*†	3·7 (1·6)*†
MCI-Other	21	480 (516)‡	60 (26)‡	579 (155)‡ §	10·7 (3·9)‡
MCI-VaD	15	476 (592)‡	60 (30)‡	567 (173)‡ ¶	10·8 (4·4)‡
MCI-DLB	3	587 (184)‖	64 (11)**	572 (121)††	8·9 (1·8)‡
MCI-FTD	1	300	51	600	11·8
MCI-SD	1	828	81	760	9·4
MCI-TBI	1	58	42	579	13·8

VaD = vascular dementia, DLB = Dementia with Lewy bodies, FTD = frontotemporal dementia, SD = semantic dementia, TBI = brain injury-induced dementia

The study furthermore shows that individuals with pathological CSF at baseline (here defined as low CSF $A\beta_{1-42}$ and high CSF T-tau) have a high likelihood to convert to dementia of the Alzheimer's type (see Figure 4 below) during the follow-up period.

Figure 4 **Kaplan-Meier Estimates of the Rate of Progression to Alzheimer's Disease in Patients with MCI Who Have Either Normal CSF or Pathological CSF at Baseline**



Note: Numbers at risk are the number of patients with MCI at each time point who had not developed any type of dementia and for whom clinical follow-up was still ongoing. Cutoff values for pathological CSF were >350 ng/L for T-tau and <530 ng/L for Aβ42 [note: exact cut-off values are assay dependent].

Low CSF $A\beta_{1-42}$ is associated with high plaque load on amyloid PET [11], with a suggestion that the changes in the CSF marker preceding PET positivity [12]. Using the selection criteria requiring a low CSF $A\beta_{1-42}$, an annual conversion rate to dementia of approximately 20% may be expected [14]. As indicated in Section 1.2, within the ADNI, CSF $A\beta_{1-42}$ was identified as the most sensitive marker for AD detection using an independent autopsy confirmed AD cohort (96.4% sensitivity, 95.2% negative predictive value, 78.6% specificity, and 81.8% positive predictive value) [9]. With longer follow-up, the incidence of a correctly identified AD-like biomarker profile at baseline is expected to increase as more patients convert to dementia. Moreover, as a follow-up of their original publication, Hansson and colleagues reported that at the study-defined cutoff, the sensitivity and specificity of Aβ42 to predict development of AD dementia within 10 years of clinical follow-up were 90% and 76%, respectively [36].

Based on the applied clinical and biomarker criteria [34], the population in this study consists with a high degree of certainty of individuals with AD in the prodromal phase who would inevitably progress to dementia in the years to come and for whom in the

prodromal phase there is no approved medication. The screening MRI will furthermore help exclude other neurodegenerative diseases (exclusion criterion 1, e.g., frontotemporal dementia) as well as extensive cerebrovascular disease (exclusion criterion 8) that could explain cognitive decline. However, since no criteria will provide absolute certainty of diagnosis, Section 4.6 states that "…the subject must be withdrawn from the study if it becomes clear that the subject's cognitive impairment is not due to AD." It is expected that this decision may be made at any time during the course of the study and that it will be based on the investigator's clinical judgment.

If gantenerumab works as expected and if halting amyloid deposition and/or removal of amyloid plaque are processes relevant to slowing disease progression, individuals in the prodromal phase of the disease might possibly benefit more than patients who have developed AD dementia already, since the intervention occurs relatively earlier in the disease process when presumably less damage to neurons has occurred.

1.3.1.1 Adjustment of CSF Aβ1-42 Cutoff

Rationale for the original CSF Aβ42 cutoff

For Study WN25203, Roche chose to use low CSF Aβ42, an indicator of amyloid pathology, along with appropriate clinical and imaging criteria, to identify subjects for treatment with gantenerumab. As the study population is very similar to that studied by the ADNI, WN25203 CSF Aβ42 inclusion criterion was based on the ADNI-defined cutoff (192 pg/mL measured by Luminex xMAP assay and based on pre-mortem CSF samples obtained from patients with autopsy-diagnosed AD and age-matched controls) [9]. Measurements of CSF Aβ42 levels for inclusion into Study WN25203 are performed at a central laboratory using a different validated assay (Innotest ELISA). To bridge between the two assay platforms *[35]*, Roche used a correlation between the Innotest ELISA and Luminex to derive the threshold level of 500 pg/mL included in the original study protocol.

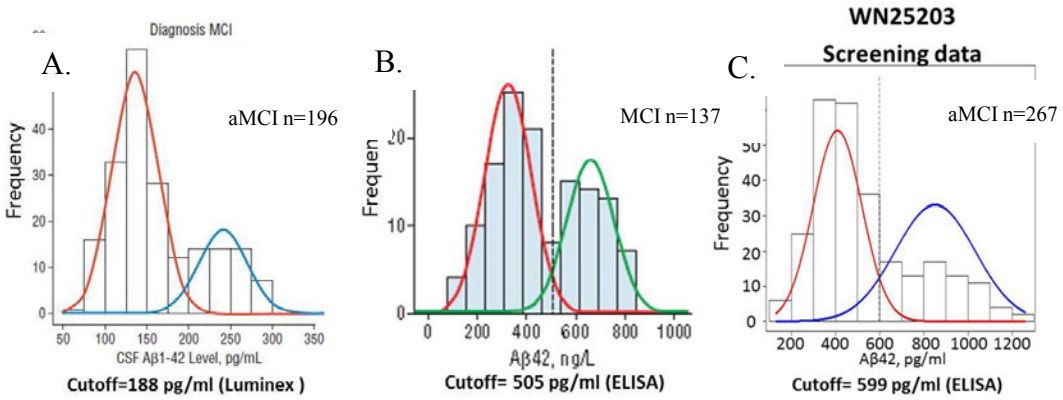
Rationale for the new CSF Aβ42 cutoff

Using ADNI CSF data, De Meyer and colleagues [37] applied a mixture modeling approach to identify two distinct AD biomarker signatures, one related to AD (low CSF Aβ42) and the other to the non-AD group (high CSF Aβ42) (Figure 5, panel A below) consistent with the current understanding that some of these individuals have MCI due to AD but others will remain stable, revert to normal, or develop dementias of other types. Remarkably, the cutoff of 188 pg/mL selected in the mixture model based on CSF Aβ42 concentration only and in the absence of any clinical data was almost identical to the value of 192 pg/mL determined by Shaw et al. using autopsy–confirmed clinical diagnoses. Such bimodal type distribution was also confirmed in a European study of MCI patients with up to 10 years clinical follow-up [36] where an unbiased "natural" cutoff was determined using the same mixture model classification (Figure 5, panel B). In this study, at this natural cutoff, CSF Aβ42 was able to predict future development of AD dementia with a sensitivity of 90% and 76% specificity.

The above clustering method was applied to screening data from all subjects screened for Study WN25203 who had CSF Aβ42 measured (269 samples up to December 21, 2011).

A similar bimodal distribution as in ADNI and the European MCI cohort (Figure 5, panel C) was observed with a natural cutoff between the two populations of 599 pg/mL, instead of 500 pg/mL, currently specified in protocol WN25203.

Figure 5 **A. Cerebrospinal Fluid–derived Aβ42 Mixture Model Applied to Individuals with Amnestic MCI from the ADNI Study**



Note: Results are shown as histograms of observed biomarker levels overlaid with the 2 mixture distributions (adapted from [37]). B. Model based clustering in European MCI study [36]. C. Model based clustering of CSF Aβ42 in WN25203

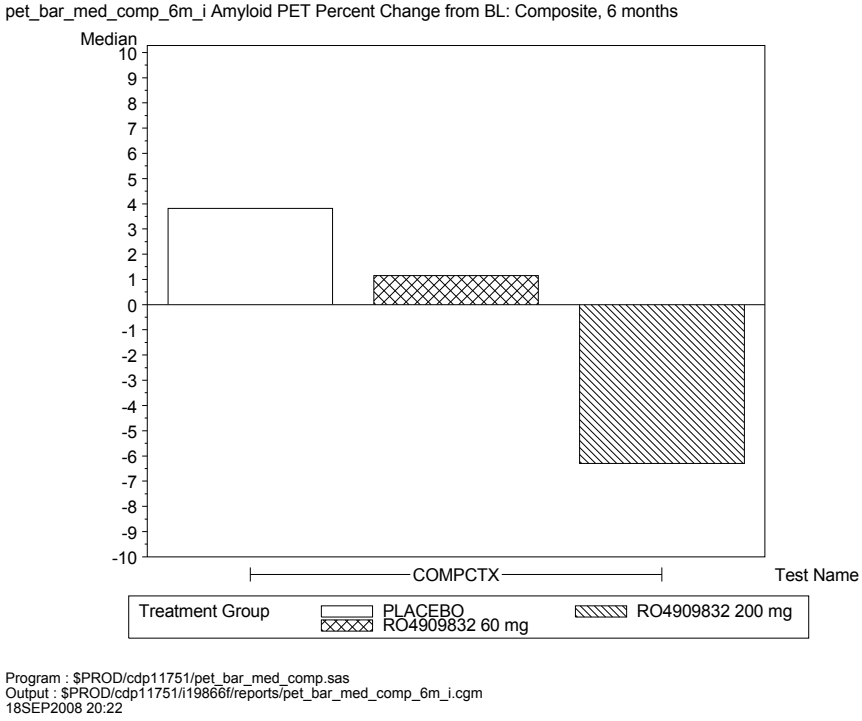
The robustness of the cutoff estimate of 599 pg/mL was evaluated by performing the model-based clustering approach using distinct subsets of the data set of WN25203 CSF screening samples, and also using snapshots of this data set at several different time points. Both analyses provided consistent estimates of the cutoff, which did not vary substantially from the cutoff value estimated based on the entire data set. In addition to the above modeling approach, Roche has obtained from its central lab an independent dataset consisting of CSF Aβ42 levels from patients diagnosed with AD (n=43) and cognitively normal age-matched controls (n=43). The patients with AD met the Diagnostic and Statistical Manual of Mental Disorders (DSM), vIII-revised criteria of dementia (1987) and the criteria of probable AD defined by NINCDS-ADRDA [15], and were also followed clinically in order to increase the clinical diagnostic accuracy [38]. At the originally defined cutoff of 500 pg/mL sensitivity and specificity were 91% and 81%, compared to 100% and 75% at the adjusted cutoff of 600 pg/ml. As the estimated assay performance at the adjusted cutoff is in line with the autopsy (gold standard) ADNI dataset (96% sensitivity and 77% specificity) [9], it appears that the proposed adjustment of the WN25203 CSF inclusion criterion will not change the population that was planned to be enrolled in Study WN25203. Thus a "natural" cutoff identified in the Study WN25203 screened population (600 pg/ml) will be used to select patients for treatment with gantenerumab.

1.3.2 Reduction in Brain Aβ by Gantenerumab

The potential benefit of gantenerumab can be anticipated from its mechanism of action which is to reduce brain amyloid. This was shown in the NN19866 MAD study in AD

patients where amyloid PET imaging was performed. Figure 6 below shows the mean change in PET tracer activity (11C-Pittsburgh Compound B [^{11}C-PIB] which indicates the amount of brain amyloid) for a composite cortical brain region of interest (including bilateral frontal, sensorimotor, lateral temporal, parietal, anterior cingulate, and posterior cingulate cortex).

Figure 6 Median Amyloid PET Percent Change from Baseline: Composite, 6 Months (ITT Population)



Since prodromal AD is considered part of the continuum of AD the amyloid removing effect of gantenerumab in patients with mild to moderate AD is expected to be relevant to the prodromal AD population in this new study. This type of positive biomarker data is probably among the strongest that could be expected in a short-term trial of a disease–modifying drug candidate and it is hoped that amyloid removal will provide benefit to individuals with prodromal AD.

The WN25203 PET substudy, which enrolled 114 participants, confirmed the findings from NN19866 MAD study (the reduction of brain amyloid by gantenerumab) using Florbetapir ^{18}F (or AV-45), a novel ^{18}F-labeled PET ligand for imaging fibrillar Aβ. A time-dependent reduction was observed with 225 mg gantenerumab in PET composite cortical SUVR with all the reference regions used. With the mean cerebellar grey cortex as the reference, after 2 years of treatment mean percent change from baseline in PET SUVR was −1.11, 0.19 and −5.37 in the placebo-, gantenerumab 105 mg- and gantenerumab 225 mg-groups, respectively (Figure 7). Following 3 years (156 weeks) of treatment, the difference was more pronounced with a 9.1% decrease in the gantenerumab 225 mg group.

PK analyses corroborated that the reduction in PET SUVR was drug concentration-dependent (i.e., subjects with higher plasma gantenerumab concentration had higher reduction in PET SUVR). Figure 8 shows PET SUVR percent changes from baseline after 2 years of treatment based on the drug exposure category with cerebellar grey cortex as the reference. No significant changes were present in the placebo- and the low concentration (1.9–5 µg/mL) gantenerumab groups; in contrast, higher gantenerumab concentration groups (5–10 µg/mL and 10–20.72 µg/mL) displayed PET SUVR reductions of up to 5% and 10%, respectively.

[redacted] This apparent inconsistency may be due to a difference between target population (moderate AD population in Study NN19866 and prodromal AD population enriched with "slow progressors" in Study WN25203) and to differences in the ligands used in study amyloid load in the brain (^{11}C-PIB and Florbetapir ^{18}F). An additional voxel-wise exploratory analysis was also performed looking at region specific treatment effects after 1 year of study treatment, using cerebellar grey matter as a reference region. An extensive anatomical network covering precuneus, ventral striatum, anterior, middle and posterior cingulate, insular, medial, and lateral prefrontal regions showed significant treatment-related SUVR reductions as compared with placebo, in both 105 and 225 mg gantenerumab treatment groups (Figure 9). At the peak voxel in precuneus, the most significant region in the voxel-wise analyses, an SUVR reduction of 15% from baseline and of 18% relative to placebo was observed in the 225 mg group. In the 105 mg gantenerumab group an 8% and an 11% reduction relative to baseline and placebo, respectively, were detected.

Figure 7 Mean Percent Changes from Baseline in Composite Amyloid PET SUVR after 2 years of Treatment (ITT Population)

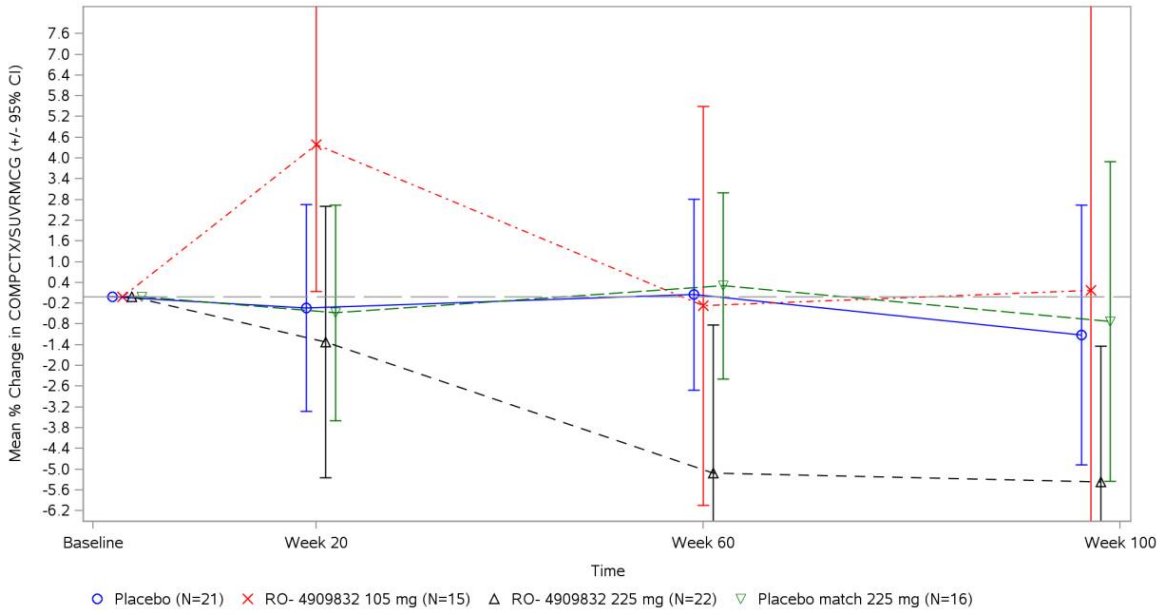
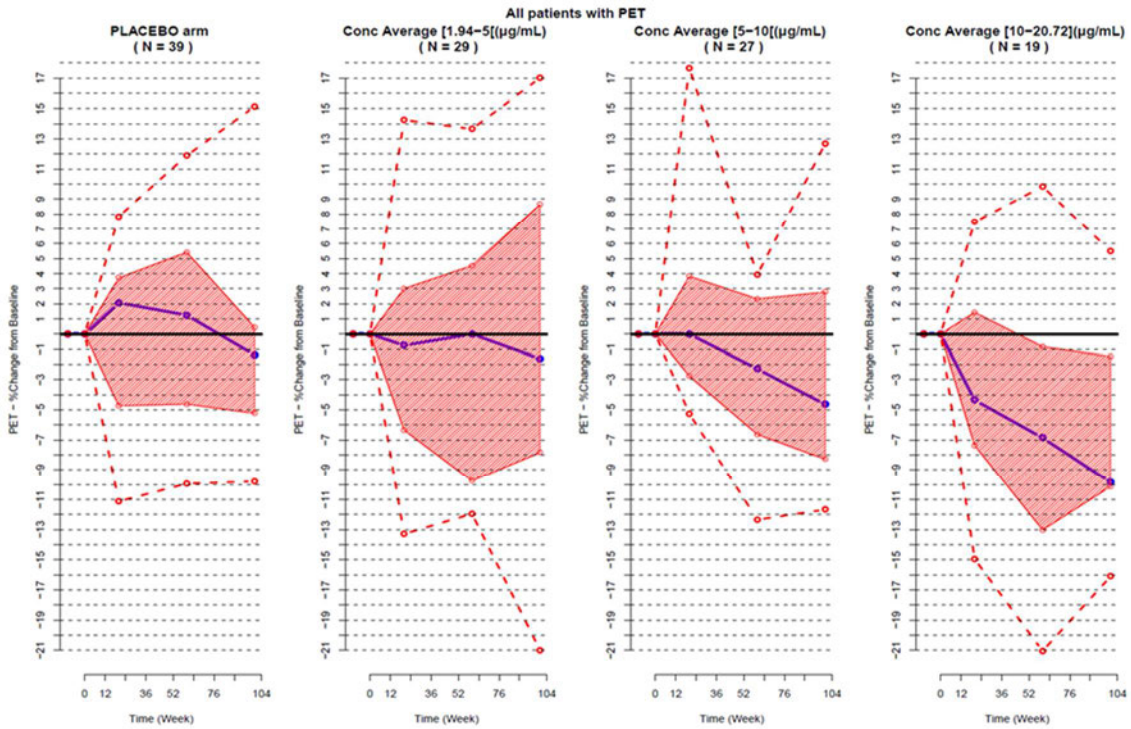
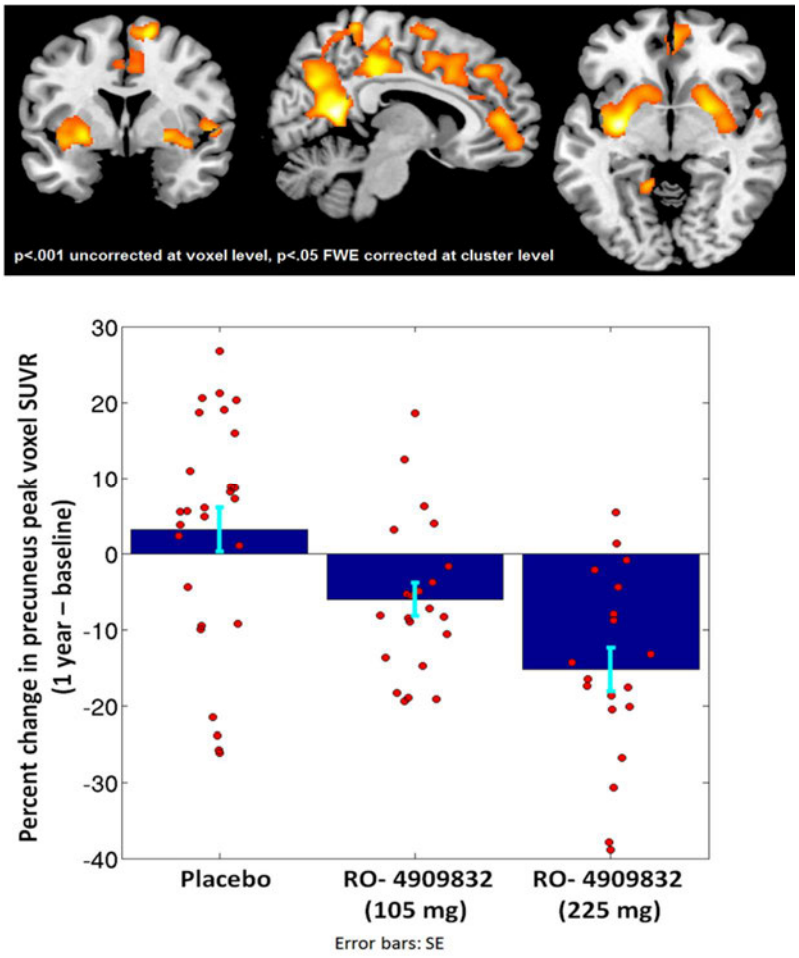


Figure 8 **Time Course PET SUVR during 2 Years of Treatment by Gantenerumab Serum Concentration Category**



Purple bold line = median; shaded = 50% observations; red dotted line = 5th and 95th percentile

Figure 9 **Voxel-Wise Changes in PET SUVR After 1 Year of Treatment with Gantenerumab**

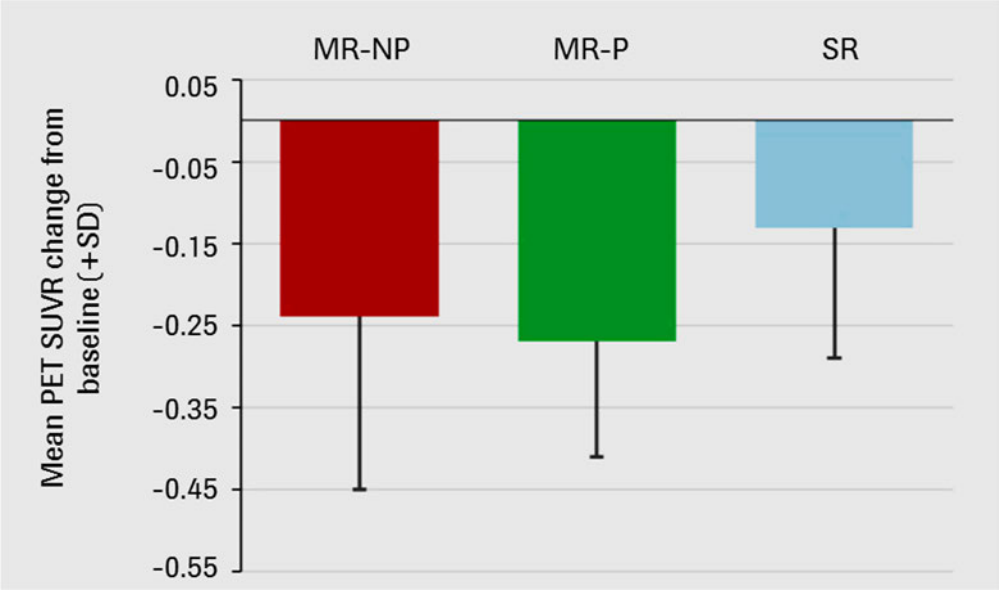


Results from the PRIME study showed dose-dependent PET composite SUVR reduction with aducanumab [42]. PK analysis demonstrated linear exposure across the aducanumab doses tested (1, 3, 6, and 10 mg/kg by IV infusion) after 26 weeks of treatment. Based on PK-PD assessment, significant covariates for amyloid removal were aducanumab exposures and baseline PET SUVR [44]. PET SUVR showed no changes or very minimal changes at Weeks 26 and 54 in the placebo and 1 mg/kg treatment arms, respectively; whereas, dose-dependent, statistically significant reductions were observed with 3 mg/kg (mean absolute change from baseline of -0.087, $p<0.01$), 6 mg/kg (-0.143, $p<0.001$) and 10 mg/kg (-0.205, $p<0.001$) treatment arms at 26 weeks as well as in the 3 mg/kg (-0.139, $p<0.001$) and 10 mg/kg (-0.266, $p<0.001$) treatment arms at 54 weeks. These reductions were also associated with clinical effects on both the MMSE and CDR-SOB with overall slowing of cognitive decline compared to placebo reaching statistical significance with the highest dose after 1 year. The difference from placebo in CDR-SOB after 1 year of treatment was -0.33, -0.71, and -1.44 ($p<0.05$) with 1, 3, and 10 mg/kg respectively.

Overall, reduction in PET SUVR corresponding to the observed clinical effect after 1 year of treatment with 10 mg/kg aducanumab, was approximately 20%. Compared to a mean PET amyloid reduction of approximately 5% achieved by 225 mg gantenerumab over 2 years, higher doses of gantenerumab will be needed to achieve the plasma concentration associated with clinically effective ~20% PET SUVR reduction.

A gantenerumab PK-PET model of amyloid reduction (details provided in [redacted]) has been confirmed by PET data from the open-label Studies WN25203 and WN28745. As of 31 August 2017, 40 patients treated with 900–1200 mg gantenerumab for ≥6 months had an OLE Week 52 PET-amyloid scan. Patients were divided into three groups for analyses purposes, on the basis of the study and on the double-blind treatment prior to switching to open-label gantenerumab and dose increase: patients in Study WN28745 treated with placebo during double-blind part (non-pre-treated), patients in Study WN28745 pre-treated (active arm during double-blind part, received gantenerumab ≤225 mg), and patients in Study WN25203 (off treatment for an approximate median of 78 weeks). Across the three groups, there was a 7%–16% reduction in PET SUVR from baseline, which was two to threefold greater than the reduction observed in the Study WN25203 double-blind PET substudy with 225 mg gantenerumab after 2 years of treatment (see Figure 7 and Figure 10). In addition, approximately one third of patients had results below the quantitative amyloid positivity threshold after 1 year of treatment with open-label gantenerumab, including a titration period and 6–9 months at higher doses (≥900 mg). Taken together, these results strongly confirm the gantenerumab mechanism of action and support selection of a target dose in alignment with the PK-PET efficacy model (see [redacted]).

Figure 10 ***Reduction of Brain Amyloid PET SUVR in Patients Exposed to at Least 900 mg for 6–9 Months in Studies WN25203 (SR) and WN28745 (MR) Open-Label Extension Studies***



MR-NP =Marguerite RoAD (Study WN28745) non-pretreated, N =14; MR-P =Marguerite RoAD (Study WN28745) pretreated, N =17; PET =positron emission tomography; SD =standard deviation.

1.3.3 MRI Findings

As described in Section 1.1.2.1, MRI findings, ARIE-E, and microbleeds were seen at 200 mg IV Q4W in the NN19866 MAD study, which was conducted in mild/moderate AD patients. The risk of ARIA-E appeared to be ApoE4 carrier status dependent.

None of the patients required any treatment for the MRI findings. All ARIA-E resolved spontaneously when treatment was discontinued.

Based on the results of the NN19866 MAD study and on knowledge about ARIAs available at the time of WN25203 study design, selection of the doses was focused on safety. As the ApoE ε4 carrier status appears to be a risk factor for the development of MRI findings, the low dose of 105 mg SC was evaluated in individuals homozygous for ApoE ε4. On the basis of total exposure (plasma AUC), this dose is comparable to the MAD dose of 60 mg IV, which was not associated with MRI findings. For individuals who are heterozygous for ApoE ε4 or non-carriers for ApoE ε4, doses of 105 and 225 mg SC were evaluated. The high dose of 225 mg SC is (based on plasma concentrations) equivalent to approximately 137 mg IV, well below the 200-mg IV dose where promptly reversible ARIA-E events were detected in the heterozygous ApoE ε4 population. [redacted] Also, additional protocol measures were put in place to mitigate any

risk due to ARIAs, including monitoring by regularly scheduled, centrally read MRIs; intensified MRI monitoring in the case of ARIA events; and, as applicable, dose modifications, temporary interruption, or permanent treatment discontinuation. All relevant new MRI findings were brought to the attention of the MRI-C (during Part 1 those were all new cases of ARIA-E, ARIA-H meeting criteria for dose modification or discontinuation, non-ARIA findings requested to be reviewed by the central reading center or sponsor, and MRI findings with associated symptoms).

In Study WN25203, out of 797 subjects who received blinded study treatment, 52 (6.5%) subjects had ARIA-E events, 2 (0.8%) subjects in the placebo group, 18 (6.6%) subjects in gantenerumab 105 mg group, and 32 (12.3%) subjects in gantenerumab 225 mg group. Over two-thirds (approximately 71%) of the ARIA-E cases occurred during the first 6 months of treatment (corresponding to 5 gantenerumab administrations): 1 (0.4%), 13 (4.8%) and 23 (8.8%), in the placebo-, gantenerumab 105 mg- and gantenerumab 225 mg groups, respectively. Approximately 75% of ARIA-E cases occurred in APOE ε4 carriers. Most of the events were asymptomatic (~90%), non-serious, resolved without consequences, and of mild severity by MRI Barkhof scoring that uses a scale from 0 (no edema) to 60 (whole brain edema) [45]. In Study WN25203, the median ARIA-E score was 3 (rated as low); only 10% of ARIA-E events were scored as >10. ARIA-E did not commonly recur in subjects who restarted treatment at half of the original dose. The findings confirmed that the risk factors for developing ARIA-E are a higher gantenerumab dose and the presence of ApoE ε4 allele (Figure 11).

One hundred fifteen (14.4%) subjects had ARIA-H findings during double-blinded treatment phase, 29 (10.9%) subjects in the placebo group, 52 (19.2%) subjects in gantenerumab 105 mg group, and 34 (13.1%) subjects in gantenerumab 225 mg group. Most of ARIA-H findings were without associated symptoms and non-serious. The time dynamic of ARIA-H followed the pattern of ARIA-E.

Figure 11 ARIA Adverse Events by APOE *ε4* Genotypes

	0ε4			1ε4			2ε4	
	Placebo (N=79)	105 mg (N=57)	225 mg (N=100)	Placebo (N=134)	105 mg (N=111)	225 mg (N=160)	Placebo (N=53)	105 mg (N=103)
ARIA-E	2 (2.5%)	1 (1.8%)	10 (10.0%)	0	6 (5.4%)	22 (13.8%)	0	11 (10.7%)
ARIA-H	5 (6.3%)	8 (14.0%)	9 (9.0%)	15 (11.2%)	19 (17.1%)	25 15.6%)	9 (17%)	25 (24.3%)

Bapineuzumab is also a monoclonal antibody with an affinity for amyloid. Similar MRI findings have been reported in a Phase 2 and Phase 3 studies [16, 46]. The majority of ARIA-E cases (69%) occurred after the first or second infusion (13 weeks apart) and were transient. An increased risk to develop ARIA-E findings was also found to be dependent on the dose and on the number of ApoE ε4 alleles [2]. The increased risk for ARIA-H were found to be associated with APOE ε4 allele frequency, pre-existing ARIA-H, treatment with bapineuzumab, and use of antithrombotic agents [47]. Homozygosity for APOE ε4 exhibited the greatest risk.

In the PRIME study, incidence of ARIA-E with aducanumab was also dose- and ApoE ε4-status–dependent. It was 5%, 5%, 43%, and 55% for 1, 3, 6, and 10 mg/kg aducanumab, respectively, versus 0% for placebo for ApoE ε4 carriers, and 0%, 9%, 11%, and 17% versus 0% among ApoE ε4 non-carriers. Most ARIA-E events (92%) were observed within the first 5 doses. MRI findings resolved typically between 4 and 12 weeks.

The exact mechanisms giving rise to ARIA remain to be fully elucidated; the frequent co-occurrence of ARIA-E and ARIA-H as observed with bapineuzumab suggests a common pathophysiological mechanism that may be related to transient increases in vascular permeability [2, 33]. Over the course of AD, vascular amyloid deposition may disrupt vascular integrity and impair perivascular pathways, leading to development of cerebral amyloid angiopathy, with age and APOE ε4 genotype being main contributors to these changes. After initiation of an anti-Aβ therapy, vessels with pre-existing amyloid vascular pathology may be transiently more susceptible to vascular extravasation events as beta amyloid is removed from the vessel wall. Also, excess amyloid accumulating in blood vessels as it is removed from amyloid plaques could also give rise to a transit increase in vascular beta amyloid, contributing to extravasation [17, 18]. Depending on the location of the vessel (intraparenchymal or meningeal), leakage of proteinaceous fluid could give rise to an increased signal detected on FLAIR images as ARIA-E in the brain parenchyma (vasogenic edema) and leptomeningeal spaces (sulcal effusions); leakage of red cells would result in ARIA-H [33]. An anti-Aβ therapy that maintains effectively vascular beta amyloid clearance would allow recovery of vascular structural integrity, and with time, the risk of such extravasation events is expected to decrease [2].

In summary, ARIA-E events in Study WN25203 were manageable, reversible, and mostly mild with the majority occurring early in treatment (with the highest frequency between 3 and 6 months). To date, substantial information is available about MRI findings and their relationship of exposure to anti-aggregated Aβ antibodies; a PK-PD model could be developed allowing a more accurate prediction of ARIA-E incidence expected with higher dose gantenerumab treatment, taking into account drug concentrations, time of ARIA-E occurrence since the first dose, and APOE ε4 genotype. The model was originally developed for bapineuzumab showing time-dependence of ARIA-E [48]. Please see [redacted] for additional information on modeling of safety outcomes.

To date, data from the OLE studies indicate that the safety profile of gantenerumab when administered in doses up to 1200 mg is comparable to the safety profile of gantenerumab in earlier studies. As of 13 February 2018, incidence of ARIA-E findings has been as expected (26% and 30.1% in Studies WN25203 and WN28745, respectively), with the majority of events being non-symptomatic and well controlled by protocol defined management rules. In a few cases, patients developed symptoms, sometimes of mild intensity (e.g., headache) and sometimes serious (e.g., confusion or seizures/epilepsy). Overall, epilepsy did not occur more frequently than expected in the AD population; however, it cannot be excluded that the presence of the ARIA-E

contributed to or triggered the onset of the symptoms. Refer to the Gantenerumab IB for additional information about ARIAs.

[redacted]

1.3.5 Risk to Subjects without AD Pathology

As an engineered monoclonal antibody, gantenerumab has an extremely high selectivity and specificity for aggregated amyloid-β and therefore gantenerumab is not expected to have any biological effect in subjects who do not have aggregated amyloid-β. However as subjects must have a low level of CSF amyloid-β at entry and this accurately selects for subjects with elevated aggregated brain amyloid, it is likely that very few subjects would be enrolled who do not have cerebral amyloid pathology and those who do not have amyloid pathology should not be at risk for MRI findings. Nevertheless and as outlined above, the study protocol applies a safety monitoring scheme that is considered to sufficiently protect all study participants as if they were at similar risk for MRI findings like AD patients.

1.3.6 Part 2 (Optional Extension Phase)

The hypothesized mechanism of action of gantenerumab is the removal of and prevention of accumulation of brain amyloid. Because this process is believed to continue throughout the course of AD, if gantenerumab has a beneficial effect on the course of prodromal AD, it is reasonable to expect that continuing therapy beyond 2 years may provide additional benefit. Regarding the time course of known adverse effects with gantenerumab, based on experience with bapineuzumab, it is likely that the risk of ARIA

decreases substantially after approximately 6 months of treatment. The other known risk factor is injection site reactions. These, however, have generally been mild and have not led to treatment discontinuation.

In Part 2, symptomatic treatments for AD will be allowed. These medications (such as donepezil and memantine) are unlikely to alter the safety profile of gantenerumab and vice versa because the adverse event characteristics are not overlapping and the pharmacological targets are different. Dosing in Part 2 of the study was terminated on 19 December 2014.

1.3.7 Part 3 (Open-Label Extension)

Since clinical efficacy may be related to both the degree of PET SUVR reduction and the timeframe over which it occurs, it is considered important to allow subjects to safely access the target dose of 1200 mg gantenerumab SC Q4W as quickly as possible, taking into account APOE ε4 status. [redacted] with ARIA-E findings seen after two to four doses as described in Section 1.1.2.1. With the implementation of the dosing regimen with gradual up-titration, subjects should be able to reach the target dose of 1200 mg safely within 10 months for APOE ε4 carriers who were on placebo or on 105 mg gantenerumab during double-blind treatment, and within 6 months for APOE ε4 carriers previously receiving 225 mg and for subjects who are non-carriers (see Sections 3.1.5.1 and 3.1.5.2). With such a titration schedule, the incidence of ARIA-E is expected to be <25%, compared to the predicted incidence of 61% in APOE ε4 carrier subjects over 2 years in the case that the target dose would be administered from the start without the up-titration regimen. The implemented protocol measures (which include dose adjustment and temporary interruption) aim to minimize the risk of MRI findings, allowing the subjects to reach the target dose in a flexible and safe manner.

The PK-PD model predicts that PET SUVR (i.e., brain amyloid load) reduction will be ~15% after 1 year of treatment with the implemented gradual up-titration schedule and ~20% after 2 years. Thus, the proposed dosing regimen attempts an optimal balance between safety and efficacy.

All subjects enrolled in Part 3 will receive active treatment and will be allowed to take symptomatic therapy.

Part 3 will only include patients who had participated in the study, either Part 1 or Part 2 prior to the futility analysis, and had at least 1 follow-up/drop-out visit after double-blind treatment (placebo or 105 or 225 mg gantenerumab SC Q4W).

1.3.8 Overall Benefit Risk Summation

The following items support the Sponsor's assessment that the overall risk-benefit for both the double-blind treatment phase (Parts 1 and 2) and the open-label extension (Part 3) of this study is favorable:

(i) Recent progress in understanding the continuum from prodromal AD to AD dementia providing the strong rationale to investigate Aβ directed therapies at the very early stage of the disease

(ii) The proven effect of gantenerumab on amyloid plaques and, thus, the potential benefit for gantenerumab to slow the onset or progression of AD with doses higher than those studied during double-blind treatment phase

(iii) The various measures taken to reduce the risk of MRI findings (including gradual up-titration in Part 3) and, if these MRI findings should develop, to rapidly identify and effectively manage them

(iv) The likelihood that ARIAs are substantially less common after approximately 6 months of treatment. During this time period, subjects are exposed to lower doses and gradually exposed to higher gantenerumab concentrations (see also [redacted]).

(v) The lack of overlap of safety characteristics between gantenerumab and symptomatic AD treatments (allowed in Part 2 and Part 3 of this study)

2. OBJECTIVES OF PART 1 (THE FIRST 2 YEARS OF THE STUDY)

2.1 Primary Objective

To evaluate the effect of 2 doses of gantenerumab versus placebo given as SC injections on the change in the CDR-SOB, a global measure of cognition and functional ability.

2.2 Secondary Objectives

To evaluate efficacy, safety, and tolerability of gantenerumab versus placebo given as SC injections using the following:

2.2.1 Cognition

Assessed with the 1) ADAS-Cog 2) MMSE, 3) the CANTAB and 4) the FCSRT-IR.

2.2.2 Global

Assessed with the CDR global score.

2.2.3 Functioning

Assessed with the FAQ.

2.2.4 Neuropsychiatric Functioning

Assessed with the Neuropsychiatric Inventory Questionnaire (NPI-Q).

2.2.5 Dementia Assessment

To determine the onset of dementia. This will be done at each of the visits when all the cognitive and functional scales are done (screening and Weeks 24, 52, 76, and 104).

2.2.6 Safety and Tolerability

Assessed by MRI, physical and neurological examinations, vital signs, blood and urine safety tests, ECGs, geriatric depression scale (GDS), Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event monitoring.

2.2.7 Brain MRI

Hippocampal volume, whole brain volume, ventricular enlargement, and possibly other volumetric measures will be assessed in an effort to detect and quantify drug effects on disease progression. Further exploratory analyses may be conducted as methods become available, in an effort to detect and quantify drug effects on disease progression.

2.2.8 Cerebrospinal Fluid Biomarkers

The effect of gantenerumab on CSF biomarkers Aβ1-42, T-tau, and P-tau will be assessed to detect and quantify drug effects on underlying disease pathology.

2.2.9 Pharmacokinetics

Plasma and CSF concentrations of gantenerumab will be quantified to explore the relationships between pharmacokinetics and other responses.

2.2.10 Anti-Drug Antibodies

The development of anti-gantenerumab antibodies (also referred to as anti-drug antibodies, ADAs, or human antihuman antibodies, HAHAs) will be assessed, and if detected, explored for their association with the PK, PD, efficacy, and safety parameters of gantenerumab.

2.3 Exploratory Objectives

2.3.1 Plasma Biomarkers

To evaluate the effect of study treatment on peripheral biomarkers of amyloid deposition and/or clearance, markers of neurodegeneration, inflammation, and other markers thought to be involved in the pathogenesis of AD.

2.3.2 Clinical Genotyping

The effect of ApoE genotype and fragmented crystalizable gamma receptor (FcγR) genotype on PK/PD/efficacy/safety parameters of gantenerumab will be assessed.

Given the association of ApoE ε4 allele and the occurrence of MRI findings seen with gantenerumab in the MAD study as well as reported for bapineuzumab, ApoE ε4 status will be used for randomizing into study treatment groups (see Section 3.1.4) and also for assignment to the titration schemes in Part 3 (see Section 3.1.5).

The Fcγ receptor will also be genotyped as it may play a role in response to IgG treatments.

2.3.3 Roche Clinical Repository

Exploratory biomarkers will be assessed in consenting subjects.

The Roche Clinical Repository (RCR) is a centrally administered facility for the long-term storage of human biological specimens. Specimens stored in the RCR will be used to:

- Study the association of biomarkers with efficacy and/ or adverse events associated with medicinal products; and/or
- Increase our knowledge and understanding of disease biology; and/or
- Develop biomarker or diagnostic assays; establish the performance characteristics of these assays.

The following sample types will be assessed in consenting subjects:

RCR DNA: may be used to explore the associations of variants of genes implicated in susceptibility and pathogenesis of AD, such as Clusterin and PICALM, and therapy response.

RCR RNA: RNA samples may be tested using techniques such as high-density microarray profiling and/or quantitative RT-PCR to study the expression profile of genes known to be involved in AD, and any other differentially expressed genes relative to treatment or dose response.

RCR plasma: may be used for exploratory biomarker analysis, including but not limited to markers of oxidative stress, neurodegeneration, inflammation or other processes involved in AD pathology.

RCR CSF: samples remaining from the mandatory analysis will be stored as RCR samples for future exploratory analysis and to support the development of biomarker and diagnostic assays.

2.4 Objectives of Part 2 (Optional Extension)

The main objectives of the study extension are to assess the long-term safety of gantenerumab as well as effects on biomarkers beyond 2 years of treatment. In addition, cognition and related measures will be assessed in Part 2; however, due to the anticipated high rate of attrition over the several years of the study, these will be exploratory outcome measures.

The following outcome measures will be assessed at select visits during Part 2, as shown in Table 3 and Table 4.

2.4.1 Cognition

Assessed with the 1) ADAS-Cog, 2) MMSE, and 3) the FCSRT-IR.

2.4.2 Global

Assessed with the 1) CDR global score

2.4.3 Functioning

Assessed with the FAQ.

2.4.4 Neuropsychiatric Functioning

Assessed with the NPI-Q.

2.4.5 Dementia Assessment

To determine the onset of dementia. This will be done at visits when all the cognitive and functional scales are done (Weeks 128, 156, 180, and 208).

2.4.6 Safety and Tolerability

Assessed by MRI, physical and neurological examinations, vital signs, blood and urine safety tests, ECGs, GDS, C-SSRS and adverse event monitoring.

2.4.7 Brain MRI

Hippocampal volume, whole brain volume, ventricular enlargement, and possibly other volumetric measures (Weeks 152, 208, and 256 [the final visit]).

2.4.8 Cerebrospinal Fluid Biomarkers

The effect of gantenerumab on CSF biomarkers Aβ1-42, T-tau, and P-tau will be assessed to detect and quantify drug effects on underlying disease pathology.

2.5 Objectives of Part 3 (Open-Label Extension)

The main objective of the open-label extension is to assess the short-term and long-term safety and tolerability of gantenerumab (RO4909832) given at doses up to 1200 mg SC Q4W (see Section 2.5.1).

The secondary objectives include the following:

1. To evaluate the effect of 1200 mg gantenerumab SC Q4W over time on imaging biomarkers (PD)
2. To evaluate the effect of 1200 mg gantenerumab SC Q4W over time on clinical outcomes (cognition and function) compared to baseline and to start of Part 3 and
3. To explore pharmacokinetics and ADAs with higher gantenerumab doses in target patient population.

2.5.1 Safety and Tolerability

- To evaluate the safety and tolerability of gantenerumab as assessed by MRI, physical and neurological examinations, vital signs, blood safety tests, ECGs, Columbia-Suicide Severity Rating Scale (C-SSRS), and adverse event monitoring

2.5.2 Brain MRI Volumetry

- To evaluate the effect of gantenerumab over time on hippocampal volume, whole brain volume, ventricular enlargement, and possibly other volumetric measures of the brain compared to baseline and to the start of Part 3. *This objective will be assessed during the initial 3 years of Part 3.*

2.5.3 Brain Amyloid Load by PET Imaging

- To assess changes in amyloid load over time using Florbetapir ^{18}F (AV-45; Amyvid™) compared to screening (if available), and to the start of Part 3. PET scans performed within 12 months prior to the first study drug administration in Part 3 will be used for the baseline of Part 3. This objective will be evaluated *during the initial 3 years of Part 3* in a subset of consenting patients participating in the PET substudy.

2.5.4 Cognition

- To evaluate the effect of gantenerumab over time *compared with baseline and with the start of Part 3* as assessed by the ADAS-Cog and the FCSRT-IR *during the initial 3 years of Part 3, and by MMSE until the end of Part 3*

2.5.5 Global Measures of Cognition and Function

- To evaluate the effect of gantenerumab over time as assessed by the CDR-SOB and CDR global score, compared to baseline and to the start of Part 3. *This objective will be evaluated during the initial 3 years of Part 3.*

2.5.6 Functioning

- To evaluate the effect of gantenerumab over time as assessed by the FAQ, compared to baseline and to the start of Part 3. *This objective will be evaluated during the initial 3 years of Part 3.*

2.5.7 Dementia Assessment

- To determine the presence of and time to the onset of dementia, according to the investigator's judgment. *This objective will be evaluated during the initial 3 years of Part 3.*

2.5.8 Pharmacokinetics

- Plasma concentrations of gantenerumab will be quantified to explore the relationships between pharmacokinetics and responses.

2.5.9 Anti-Drug Antibodies

- The development of anti-gantenerumab ADAs will be assessed and, if detected, explored for their association with the PK, PD, efficacy, and safety parameters of gantenerumab.

3. STUDY DESIGN

3.1 Overview of Study Design and Dosing Regimen

This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study, followed by open-label extension with active study drug treatment.

In Part 1 subjects will be selected who meet criteria of memory impairment and have reduced CSF $A\beta_{1-42}$ levels. These requirements will select subjects with a high likelihood of prodromal AD who are in the pre-dementia phase of Alzheimer's disease. SC study treatment will be given Q4W for 26 administrations so the total treatment duration is 104 weeks or approximately 2 years.

Subjects who complete Part 1 of the study through the Week 104 visit may continue in to the optional Part 2 where they will continue to receive blinded treatment Q4W for up to 2 additional years.

Subjects who complete the double-blind treatment period (Part 1 or both Parts 1 and 2), as well as subjects who prematurely discontinue double-blind treatment at any time during the study, will be asked to return for the follow up visits 4 and 12 weeks after the last dose of double-blind study treatment, and for an optional visit 1 year (52 weeks) after the last dose of double-blind study treatment.

All subjects who were eligible for and enrolled into Study WN25203 and had at least 1 follow-up/drop-out visit after double-blind treatment (placebo or 105 or 225 mg gantenerumab SC Q4W) will be offered participation in an open-label extension (Part 3) during which they will be treated with higher gantenerumab doses (up to 1200°mg gantenerumab SC) Q4W *initially* for *an* additional 3 years, unless exempted for the criteria listed in Section 4.4. *All subjects who complete 3 years of open-label treatment will be given the option to continue receiving gantenerumab until July 2020 (up to 19 additional months).*

Subjects will undergo brain MRI exams for monitoring safety and response to study treatment. Subjects will also undergo common tests of safety as well as tests of cognition and other clinical scales commonly used when monitoring subjects likely to develop dementia.

3.1.1 Use of Symptomatic Treatments for AD in Part 1

Approved agents for the symptomatic treatment of AD are AChEIs and memantine. These agents are not to be taken for 2 months prior to signing of the Informed Consent Form (ICF) and are not permitted at entry to or during Part 1 of the study through the Week 104 or Drop-Out 1 visit. This is the case even for subjects who develop dementia of the Alzheimer's type during Part 1 of the study. These agents are not approved for prodromal/pre-dementia AD (clinically MCI) and several studies of multi-year durations have failed to show they delay the onset of dementia, which tends to suggest their effects, once dementia is first diagnosed, are likely to be minimal [19].

Though it has been well established that there is a cholinergic deficiency in the brains of patients with advanced AD, it is controversial whether there is significant cholinergic deficiency in MCI or early AD. Two recent imaging studies with different tracers have not shown a reduction in nicotinic receptors in MCI (MMSE 26.8 SD 2.3) or early AD (MMSE 22.5 SD 2.5). These articles discuss and reference other studies that suggest that cholinergic deficits are not a prominent feature of MCI or early Alzheimer's disease [20, 21]. In addition, a recent postmortem study showed no decrease in cholinergic projections to the cortex in MCI subjects (MMSE range 22–28). However, there was a

decrease in the mild-to-moderate AD group (MMSE range 14–25), which correlated with impairment on the MMSE, Global Cognitive Score, and frontal lobe functioning [22].

Though AChEIs are, for most subjects, likely to provide little or no benefit during the period of this study, an additional reason for not allowing them to be added on prior to completion of the first follow-up visit is that this will interfere with evaluating whether gantenerumab has an effect on disease progression. As an example of this, if gantenerumab does slow the progression of prodromal AD, a disproportionately greater number of placebo subjects are likely to receive an AChEI and even though the agent may have little or no effect on cognition in MCI or early AD many of these subjects are likely to improve mainly due to a "placebo response" which will diminish any treatment difference between placebo and gantenerumab. Such biased estimates of treatment difference cannot properly be addressed by any statistical analysis methods. A recent publication of a 48-week study of one of these agents (donepezil) in MCI (MMSE of 24–28) showed a prominent placebo effect but did not show benefit of donepezil based on the primary endpoint [23]. The study reported a small but significant benefit of less than 1 point on the ADAS-Cog in the last observation carried forward (LOCF) analysis. However, as pointed out in a subsequent letter to the editor, this may be an artifact of significantly more donepezil subjects stopping treatment early, and the LOCF scores used in the analysis are likely to be better than the scores would have been had they stayed in the study for 48 weeks [24]. Overall about 42% of the donepezil group discontinued treatment early compared to 29% for placebo and of these, discontinuations due to adverse events were 18% for donepezil and 8% for placebo. As commented in the article, MCI subjects may be less tolerant of these agents than patients with AD. This would be an additional rationale for excluding these agents at trial entry or as added on during the trial as they would likely increase the incidence of adverse events and dropouts and may require adjustment of the symptomatic treatment which will further complicate the evaluation of effects of the study treatment on disease progression.

3.1.2 Use of Symptomatic Treatments for AD in Part 2

Subjects who continue into Part 2 of the study may start approved symptomatic AD treatments after the Week 104 assessments have been completed at the discretion of the Principal Investigator.

3.1.3 Use of Symptomatic Treatments for AD in Part 3

Use of any approved symptomatic treatments for AD is allowed in Part 3 at the discretion of the Principal Investigator.

3.1.4 Rationale for Dose Selection Parts 1 and 2

Based on the results of the MAD study, the doses to be evaluated will depend on the ApoE genotype of the subject in order to minimize the possibility of MRI findings.

3.1.4.1 Dosing in Subjects Who Are 0ε4 and 1ε4

At 200 mg IV in the MAD study, of the 3 patients who were 0ε4, the only MRI finding was 1 microbleed (first seen at treatment follow-up and not seen at subsequent MRI) and of the 11 who were 1ε4, 3 had MRI findings of which 1 was probably a small ischemic

area and 2 were MRI findings suggesting "inflammation or vasogenic edema" (which in these cases were asymptomatic and resolved rapidly after treatment was suspended).

Given (i) the asymptomatic nature of these MRI findings together with the prompt reversibility of the FLAIR findings and the fact that the single microbleed was seen during the follow-up period (off treatment and within expected background incidence of microbleeds in this population), plus (ii) the absence of MRI findings in the 60 mg MAD dose cohort which included six 0ε4 and six 1ε4, plus (iii) the MRI monitoring schedule implemented in this study, SC doses equivalent to approximately 130 mg IV and 60 mg IV (based on plasma gantenerumab AUC) will be administered every 28 days to subjects with genotypes 0ε4 and 1ε4.

[redacted], the doses of 105 mg and 225 mg have been selected. Results from the SC bioavailability study (Section 1.1.2.2) demonstrated that based on AUC comparison, these SC doses of 105 mg and 225 mg would translate into [redacted], respectively. Therefore, subjects who are 0ε4 or 1ε4 will receive placebo, 105 mg ([redacted]) or 225 mg ([redacted]).

3.1.4.2 Dosing in Subjects Who Are 2ε4

Subjects who are 2ε4 will receive either placebo or 105 mg. In the MAD, no MRI effects were seen in the 3 subjects who were 2ε4 at 60 mg IV. However because both subjects who were 2ε4 at 200 mg had prominent findings it has been decided to be more cautious with this group and to apply only the lower dose of 105 mg SC.

Also supporting dose selection for this study are the PET data available from the MAD study as mentioned in Section 1.1.2.1, suggesting an amyloid-removing effect of gantenerumab over the period of up to 6 months at doses of 60 and 200 mg IV with the effect at the higher dose appearing larger. It is uncertain whether brain amyloid removal will result in clinical efficacy; however, the MAD data, together with the known preclinical profile of gantenerumab, suggest that the doses used in this Phase 3 study may lead to the desired amyloid-removing effect.

3.1.5 Rationale for Dose Selection for the Open-Label Extension (Part 3)

As described earlier in Sections 1.2.3, 1.3.3, and 1.3.7, PK-PD *(PK-PET)* models for anti-aggregated Aβ have been developed to extrapolate clinically effective gantenerumab doses and to predict dosing regimens with up-titration to reduce the incidence of MRI findings. Based on the results of the PRIME study, statistically significant clinical effects of aducanumab were present at 10 mg/kg IV Q4W, associated with ~20% reduction in composite amyloid PET SUVR after 2 years. The equivalent gantenerumab dose to achieve this SUVR reduction was predicted as 1200 mg SC Q4W. Additional information on population PK-PET response analysis of gantenerumab and aducanumab can be found in [redacted].

Safety outcomes at doses higher than the 225-mg dose (the highest gantenerumab dose tested in Phase 3) were projected from the results of the double-blind treatment period of Study WN25203 and from the PRIME study, using a bapineuzumab-based model [48],

taking into consideration known risk factors for ARIA-E: drug concentrations, time since the first dose, and APOE ε4 allele status. Gradual exposure to gantenerumab is predicted to be linked with an acceptable incidence of ARIA-E, mostly occurring during the first months of treatment. The starting dose of gantenerumab and the titration schedule will be adapted to the presence of APOE ε4 allele and to the dose of gantenerumab received during Parts 1 and 2 (Table 5 and Table 6).

3.1.5.1 Dosing in APOE ε4 carriers (1ε4 and 2ε4 genotypes) previously on placebo, 105 mg gantenerumab, and 225 mg gantenerumab meeting criteria for dose reduction due to ARIAs:

- Doses 1, 2, and 3: 105 mg SC
- Doses 4, 5, and 6: 225 mg SC
- Doses 7 and 8: 450 mg SC
- Doses 9 and 10: 900 mg SC
- Dose 11 onwards: 1200 mg SC

The above titration schedule will allow subjects to reach the target dose of 1200 mg gantenerumab within 10 months and is predicted to result in an ARIA-E incidence close to 25% in subjects carrying APOE ε4 allele, compared to 61% expecting to occur without up-titration by starting with 1200 mg gantenerumab.

3.1.5.2 Dosing in APOE ε4 non- carriers (0ε4 genotype) and in APOE ε4 carriers receiving 225 mg gantenerumab until the end of double-blind treatment (1ε4 genotype):

- Doses 1 and 2: 225 mg SC
- Doses 3 and 4: 450 mg SC
- Doses 5 and 6: 900 mg SC
- Dose 7 onwards: 1200 mg SC

The above titration schedule will allow the subject to reach the target dose of 1200 mg gantenerumab within 6 months.

3.2 End of Study

The end of the study will be considered to be the date of the last visit (including the last scheduled follow-up visit according to the study protocol) of the last subject in the study.

3.3 Number of Subjects / Assignment to Treatment Groups in Part 1

The planned total number of subjects is approximately 770, 256 on placebo and 257 on each of the two gantenerumab doses. Based on the ADNI data the approximate genotype distribution is expected to be 33% 0ε4, 50% 1ε4, and 17% 2ε4 (with respective N's of: 257, 385, and 128). Subjects with ApoE genotypes 0ε4 or 1ε4 will be randomized to gantenerumab 105 mg, 225 mg, or placebo. Subjects with ApoE genotype 2ε4 will be assigned to gantenerumab 105 mg or placebo. Within each of the three ApoE genotype groups (0ε4, 1ε4, or 2ε4) subjects will be assigned to either gantenerumab or placebo in 2:1 ratio. Additional information is given in Section 6.4.

3.4 Centers

Approximately 150–200 centers will participate in the study.

4. STUDY POPULATION

Under no circumstances were subjects enrolled in this study (in Parts 1 and 2) permitted to be re-randomized to this study and enrolled for a second course of double-blind treatment. Subjects who were eligible for and enrolled into Study WN25203 and had at least 1 follow-up/drop-out visit after double-blind treatment (placebo or 105 or 225 mg gantenerumab SC Q4W) will be offered participation in an open-label extension (Part 3).

4.1 Overview

The population will consist of subjects with prodromal AD who were not receiving memantine or cholinesterase inhibitors and have not been treated with these agents for at least 2 months prior to signing the ICF for Part 1.

4.2 Inclusion Criteria

A subject may be included if the answer to all of the following statements is "yes."

1. Written consent signed by the subject (co-signed by the subject's next of kin or study partner, if required by the local regulations/guidelines/Ethics Committee [EC]/Institutional Review Board [IRB])
2. Age: 50–85 at the time of signing the ICF
3. Males and females. Females must be either:
    - Of non-childbearing potential (more than 2 years after the cessation of menses or surgically sterile by means of hysterectomy, bilateral oophorectomy, or tubal ligation). Additional blood tests will be done if required by the local regulations/guidelines/EC/IRB for further confirmation of non-childbearing potential or –
    - If she is of childbearing potential, she must:
    - Have a negative urine pregnancy test at screening and a negative urine pregnancy test at baseline.
    - Agree to use two methods of contraception from the screening visit until 16 weeks after study drug discontinuation. Of the two contraceptive methods, one must be from Group 1, and one must be from Group 2, defined as follows: Group 1: Oral, implantable, trans-dermal or injectable hormonal contraceptives, intrauterine devices, or partner's sterilization (vasectomy). If a hormonal contraceptive will be chosen from this group, it must have been taken for at least 1 month prior to randomization. Group 2: Condoms, diaphragm or cervical cap, all in combination with spermicide. Abstention and rhythm methods are not acceptable methods of contraception.
4. Has a study partner, who in the investigator's judgment has frequent and sufficient contact with the subject so as to be able to provide accurate information as to the subject's cognitive and functional abilities, who agrees to provide information at clinic visits which require partner input for scale completion, and who signs the necessary consent form if applicable.

5. Fluent in the language of the tests used at the study site
6. Mental retardation has been excluded by the investigator. This may be based on, for example, sufficient education or work experience
7. Willing to complete all aspects of the study (including MRI, lumbar puncture [LP], and genotyping) and capable of doing so either alone or with the help of the study partner
8. Have not received within the past 2 months and are not currently being treated with approved marketed medications for AD and the study physician does not anticipate any treatment with one during the study
9. If not already aware, willing to have their ApoE genotype status withheld until the study is unblinded unless required by the relevant health authority or EC/IRB. If informing the subject of their ApoE status is required, the informed consent may be reviewed and re-signed before treatment begins.
10. Visual and auditory acuity sufficient to perform the cognitive tests (eye glasses and hearing aids are permitted.)
11. Agree not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose

Cognition-related and test-based inclusion criteria indicating the subject has prodromal AD

12. Study partner has noticed a recent gradual decrease in the subject's memory (e.g., over the prior 12 months), which the subject may or may not be aware of.
13. Abnormal memory function at screening or 1 month prior to screening based on the FCSRT-IR of
    - free recall <17, or
    - total recall <40, or
    - [free recall <20 and total recall <42].
14. Screening MMSE score of 24 or above.
15. Screening global CDR of 0.5 with a memory box score of 0.5 or 1.
16. Aside from memory impairment, general cognition and functional performance are largely preserved such that a diagnosis of AD with dementia cannot currently be made.
17. Modified Hachinski Ischemia Scale score of ≤4
18. CSF $A\beta_{1-42}$ level ≤600 ng/L as measured by the central laboratory. Individuals who do not meet this criterion may not be re-screened for this study.

4.3 Exclusion Criteria

A subject will be excluded if the answer to any of the following statements is "yes."

CNS Disorders

1. Other prior or current neurologic or medical disorder which may currently or during the course of the study impair cognition or psychiatric functioning including but not limited to: head trauma, seizure disorder, neurodegenerative disease, hydrocephalus, cerebral / spinal hematoma, inflammatory disease, CNS infection (e.g., encephalitis or meningitis), neoplasm, toxic exposure, metabolic

disorder (including hypoxic or hypoglycemic episodes), or endocrine disorder. If one of these disorders is suggested by the central reading of the baseline MRI, the subject may be included after consensus agreement between the investigator and the study director that the subject is still considered to have prodromal AD.

2. A history of stroke
3. A documented history of transient ischemic attack within the last 12 months
4. History of schizophrenia, schizoaffective disorder, or bipolar disorder
5. Currently meets criteria for major depression
6. Any other psychiatric condition/disorder which could significantly interfere with the subject's cooperative participation (e.g., prominent anxiety, agitation, or behavioral problems)
7. Current evidence or history of substance abuse disorder (DSM-IV) within 2 years, except, nicotine use is allowed.

Imaging-Related Criteria

8. As assessed by the central reader, MRI evidence of a) more than one lacunar infarct, b) territorial infarct or macroscopic hemorrhage, or c) any deep white matter lesion corresponding to an overall Fazekas score of 3 which requires at least 1 confluent hyperintense lesion on the FLAIR sequence which is 20 mm or greater in any dimension
9. The combined number of ARIA-H (microbleeds and areas of leptomeningeal hemosiderosis) on MRI is more than 2 on a 1.5T machine or more than 3 on a 3T machine based on the review done by the central reader.
10. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, foreign metal objects in the eyes, skin or body or any other circumstance which would contraindicate an MRI scan or significantly impair MRI image quality based on review by the central reader.

Cardiovascular Disorders

11. History of atrial fibrillation except if only one episode which resolved more than three years ago and for which treatment is no longer indicated
12. Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, New York Heart Association Class II or more cardiac failure)
13. Average QT interval corrected with Fridericia's equation (QTcF) above 470 msec based on a set of three good quality ECGs, or clinically relevant abnormalities on screening ECG based on centralized reading (e.g., multifascicular block; left bundle branch block, AV block II)
14. Uncontrolled hypertension (i.e., blood pressure generally >160 systolic or >95 mmHg diastolic)

Hepatic/Renal Disorders

15. Screening AST or ALT ≥2 or total bilirubin ≥1.5 times the upper limit of normal (ULN) which is still above these limits if retested due to a slightly elevated initial result

16. Screening creatinine clearance <30 mL/min as calculated by the central lab using the Cockcroft-Gault formula, which remains <30 mL/min if retested

Infections/Immune Disorders

17. History of HIV infection, history of Hepatitis B infection within the past year, history of Hepatitis C infection which has not been adequately treated or history of spirochete infection of the CNS, (e.g., syphilis, lyme, or borreliosis)
18. Autoimmune disease which is debilitating or potentially debilitating (e.g., Lupus, multiple sclerosis). Rheumatoid arthritis may be allowed if, in the opinion of the investigator, it will not put the subject at increased risk or interfere with the interpretation of the study.
19. Immunocompromised systemically due to continuing effects of immune suppressing medication

Metabolic/Endocrine Disorders

20. Screening thyroid function tests are abnormal such that a new treatment or an adjustment of current treatment is required. The subject may be rescreened if there is no improvement in cognition after 3 months of adequate treatment.
21. Folic acid or B12 levels (current or within the past 6 months) that are sufficiently low such that deficiency may be contributing to cognitive impairment. In such cases the subject may be rescreened if there is no improvement in cognition after 6 months of appropriate treatment.
22. Screening hemoglobin A1C (HbA1C) >8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes). The subject may be rescreened after 3 months to allow optimization of diabetic control.
23. Body mass index ≥36

Other

24. Deformity of the lumbosacral spine which would contraindicate a lumbar puncture
25. Screening prothrombin time (PT) is abnormal and remains abnormal when retested.
26. History of cancer except if considered likely to be cured or in the case of prostate cancer there has been no significant progression over the last 2 years.
27. Any other medical condition not previously mentioned that could be expected to progress, recur, or change to such an extent that it could bias the assessment of the clinical or mental status of the subject to a significant degree or put the subject at special risk or any pre-planned surgery, other than minor procedures.
28. Clinically significantly abnormal screening blood, urine, or CSF which remain abnormal on retest
29. Currently or within the last 1 month participated in a non-pharmacological trial with a key objective of improving cognition
30. Residence in a skilled nursing facility such as a convalescent home or long-term care facility

Medications

31. Ever participated in a study of gantenerumab
32. Ever participated in a study of a vaccine or other long-acting biological agent which was being evaluated to prevent or postpone cognitive decline
33. Received any other investigational treatment within 3 months of screening or 5 half-lives, whichever is longer.
34. Received within 2 months of screening a cholinesterase inhibitor**,** memantine, or Souvenaid®
35. Within 1 month of screening:
    a) Started taking ginkgo biloba, lecithin, vitamin B12, or any other agent or supplement intended to improve cognition or reduce cognitive decline
    b) Received medication for systemic immunosuppression including corticosteroids
    c) Received medication used to treat Parkinsonian symptoms or any other neurodegenerative disorder even if it is being taken for a non-neurodegenerative disorder such as restless legs disorder
    d) Received medication that may currently be contributing to cognitive impairment (e.g., clonidine, alphamethyldopa)
    e) Received an antipsychotic or a neuroleptic medication except as brief treatment for a non-psychiatric indication (e.g., emesis)
    f) Received medication used to treat a mood or anxiety disorders except if it is a selective serotonin reuptake inhibitor (SSRI), selective norepinephrine reuptake inhibitor (SNRI), selective serotonin/norepinephrine reuptake inhibitor (SSNRI), bupropion, buspirone, mirtazapine, or trazadone and is given as maintenance treatment
    g) Received anti-hemostasis medication (e.g., warfarin) *except* low-dose aspirin (dose depends on local practice but preferably 100 mg or less)
    h) Received medication with anticholinergic activity that may impair cognition or attention (e.g., centrally acting antihistamines or anti-spasmodics) *except* if used only intermittently (generally no more than twice per week) and there has been no use within the 4 days before the screening cognitive testing
    i) Received anticonvulsant medication except if for an approved pain indication
    j) Received narcotic analgesics except if typically on 4 or fewer days per month for a self-limited pain indication (e.g., migraine) or if used for cough or diarrhea (e.g., codeine) and there has been no use within the 4 days before the screening cognitive testing
    k) Received sedative, hypnotic, or benzodiazepine medication except if used only intermittently (generally no more than twice per week). For example, use of a short-acting benzodiazepine-like medication (e.g., zolpidem) or trazadone for sleep and lorazepam for occasional mild anxiety are allowed. These medications may not have been taken within the 4 days before the screening cognitive testing

36. For the medication exceptions listed just above, any change in the prescribed regimen within the last month.

4.4 Eligibility for the Open-Label Extension (Part 3)

Subjects who received double-blind treatment during either Part 1 or Part 2 prior to the futility analysis, and had at least one follow-up/drop-out visit will be eligible to enter Part 3. For reasons related to subject safety, subjects who meet any of the following criteria will not be eligible for Part 3:

- Prematurely discontinued from Parts 1 and 2 for safety reasons affecting participation in the study (e.g., MRI findings meeting criteria for treatment discontinuation in Parts 1 and 2)
- [redacted]
- Received another investigational medication after the end of double-blind treatment
- Participation in Part 3 deemed inappropriate by investigator or Sponsor (eg, any serious medical condition or abnormality in clinical laboratory tests that precludes the patient's safe participation in the open-label extension).

4.5 Concomitant Medication and Treatment

Adding a new medication or changing the dose of a medication after signing the informed consent form should only occur for the treatment of an adverse event. Exceptions to this include: 1) preventive medication such as prophylactic use of an anti-infective or vaccination 2) medication for a pre-existing condition which has not worsened, or 3) temporary use or withholding of medication to help carry out certain study procedures (e.g., LP, MRI or PET scan).

Adding a new vitamin regimen or dietary supplement during double-blind treatment (Parts 1 and 2) is discouraged. Any medications that are used intermittently that may affect cognition such as a narcotic analgesics, hypnotics, or anxiolytics should be avoided as much as possible prior to the scheduled assessments of cognition. If such a medication is required, sufficient time must have passed (preferably 4 or more days) so that the effect of the medication will not interfere with the assessment. Anxiolytics may be given prior to an MRI, PET scan, or LP; however, cognition testing should not be done until sufficient time has passed for the effects to have diminished.

If the subject requires treatment with a medication listed in the exclusion criteria, a medication listed as an exception above should be used if possible and appropriate (i.e., for depression an SSRI and not a tricyclic). If the subject requires treatment that is not listed as an exception, the subject may need to be withdrawn from the trial (e.g., warfarin as an anticoagulant, anti-Parkinson medication, antipsychotic medication or continuous treatment with narcotics). In these cases, the investigator should inform and consult with the Sponsor.

Of special note, if a subject is to be started on a cholinesterase inhibitor, memantine, or Souvenaid during Part 1 of the study prior to completion of the visit at Week 104, the subject will need to be withdrawn from the study. These medications should be withheld until after the Week 104 or first drop-out (DO1) is completed. However, for subjects

entering Part 2 of the study, these medications may be started after the Week 104 assessments have been completed if judged appropriate by the Principal Investigator. These medications will be permitted at any time in Part 3.

4.6 Criteria for Premature Withdrawal

In addition to withdrawals described above for concomitant medication, the subject must be withdrawn from the study if it becomes clear that the subject's cognitive impairment is not due to AD. Subjects do not have to be withdrawn from the study if they develop dementia. However, they do need to be withdrawn if prohibited AD medications will then be started prior to completion of the Week 104 or first drop-out (DO1) visit.

Subjects have the right to withdraw from the study at any time for any reason.

In the case that the subject decides to prematurely discontinue study treatment ["refuses treatment"], he/she should be asked if he/she can still be contacted for further information concerning their reasons for discontinuing and will be asked to return at 4 weeks, 12 weeks, and, optionally, 1 year (52 weeks) from the time of their last dose of study drug in Parts 1 and 2 (see Table 2, Table 3, and Table 4), and 4 weeks after the end of treatment in Part 3 (see Table 8 *and Table 9*). The outcome of that discussion should be documented in the medical records. If lost to follow-up, the investigator should contact the subject or a responsible relative by telephone followed by registered mail or through a personal visit to establish as completely as possible the reason for the withdrawal. A complete final evaluation at the time of the subject's withdrawal should be made with an explanation of why the subject is withdrawing from the study.

Subjects should be informed of circumstances under which their participation may be terminated by the investigator without the subject's consent. The investigator may withdraw subjects from the study in the event of intercurrent illness, adverse events, lack of compliance with the study and/or study procedures (e.g., dosing instructions; missing more than three consecutive doses, or more than six study visits in a calendar year for no other reason than compliance), or any reason where it is felt by the investigator that it is in the best interest of the subject to be terminated from the study. Any administrative or other reasons for withdrawal must be explained to the subject.

If the reason for removal of a subject from the study is an Adverse Event, the principal specific event will be recorded on the AE eCRF. The subject should be followed until the Adverse Event has resolved, if possible.

An excessive rate of withdrawals can render the study non-interpretable; therefore, unnecessary withdrawal of subjects should be avoided. Should a subject decide to withdraw, all efforts will be made to complete and report the observations prior to withdrawal as thoroughly as possible.

4.6.1 Withdrawal from Study Drug

Study treatment must be discontinued for protocol-specific rules implemented for subject safety. The pre-specified criteria for withdrawal from the study drug include the following:

- Pregnancy (see Section 7.2.3)

- MRI findings (see Section 5.1.6.1 for Part 3)

In addition, study treatment may be also modified or discontinued based on MRI-C recommendations and/or iDMC recommendations (during double-bind treatment period), as deemed necessary (Section 10.1)

4.6.2 Withdrawal of Subjects from the Roche Clinical Repository (RCR)

Subjects who gave consent to provide RCR specimens have the right to withdraw their specimen from the RCR at any time for any reason. If a subject wishes to withdraw his/her consent to the testing of his/her specimen(s), the investigator must inform the Roche monitor in writing of the subject's wishes using the RCR Subject Withdrawal Form. A subject's withdrawal from the main trial does not, by itself, constitute withdrawal of the specimen from the RCR. Likewise, a subject's withdrawal from the RCR does not constitute a withdrawal from the main trial.

4.7 Replacement Policy [Ensuring Adequate Numbers of Evaluable Subjects]

4.7.1 For Subjects

Subjects prematurely discontinued from the study will not be replaced.

4.7.2 For Centers

A center may be replaced for the following administrative reasons:

- Excessively slow recruitment.
- Poor protocol adherence.
- Non-GCP compliance or any significant audit findings

5. SCHEDULE OF ASSESSMENTS AND PROCEDURES

Table 1 Schedule of Assessments – First Year

Visit by week #	Screen	Baseline	1	4	8	12	16	20	24	28	32	36	40	44	48	52	53
Dose Number	**(8 wks)**	**1**		**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	
Demographics[12]	X																
Medical/surgical history	X																
Physical Exam	X															X	
Neurological Exam	X															X	
Modified Hachinski	X																
Clinical Genotyping	X																
RCR Plasma and RNA	X[6]																X
RCR DNA	X[6]																
Vital Signs	X	P	X	P	P	P	P	P	P	P	P	P	P	P	P	P	X
ECG (triple if underlined)	X	P	X		P			P			P			P			X
Blood and Urine Labs	X[10]	P	X		X			X			X			X			X[10]
Urine Pregnancy Test[5]	X	P		P	P	P	P	P	P	P	P	P	P	P	P	P	
PK plasma		P	X		P			P						P			X
ADA samples		P	X		P			P						P			
Plasma Biomarkers		P						P						P			
CDR	X	P-1 wk							P							P	
FAQ, NPI-Q, GDS	X	P-1 wk							P							P	
MMSE	X	P-1 wk				P			P			P				P	
Dementia Assessment	X								P							P	
ADAS-Cog	X	P-1 wk				P			P			P				P	
FCSRT-IR	X[4]	P-1 wk				P						P					
CANTAB	X	P-1 wk							P							P	
C-SSRS		P-1wk		X	X	X	X	X	X	X	X	X	X	X	X	X	
LP/CSF, plasma PK and matching serum sample[3]	X[2]															10/20d[2]	
RCR CSF	X															10/20d[2]	
MRI	X[2]			10/20d	*	10/20d	*	10/20d	*		10/20d	*		10/20d	*		

Table 2 Schedule of Assessments – Second Year

Visit by week #	56	60	64	68	72	76	80	84	88	92	96	100	101	FU1/104[7]	FU2/112	FU3/152	Unsch.[1]	FU1/DO1	FU2/DO2	FU3/DO3[12]
Dose Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**								
Physical Exam															X	X	X		X	X
Neurological Exam															X	X	X		X	X
RCR Plasma and RNA														X[6]				X[6]		
Vital Signs	P	P	P	P	P	P	P	P	P	P	P	P	X	X	X	X	X	X	X	X
ECG (triple if underlined)				P				P				P	X		X		X		X	
Blood and Urine Labs				X			X					X	X[10]		X	X	X	X[10]	X	X
Urine Pregnancy Test[5]	P	P	P	P	P	P	P	P	P	P	P	P			X		X		X	
PK plasma				P								P	X		X		X		X	
ADA samples				P								P			X		X		X	
Plasma Biomarkers				P								P			X		X		X	
CDR			P			P			P					X		X	X	X		X
FAQ, NPI-Q, GDS						P								X		X[11]	X	X		X[11]
MMSE			P			P			P					X			X	X		
Dementia Assessment						P								X			X	X		
ADAS-Cog			P			P			P					X			X	X		
FCSRT-IR			P						P					X			X	X		
CANTAB						P								X			X	X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X		X	X		X	X	X	
LP/CSF, plasma PK and matching serum sample[3]														10/20d[2]			X	10/20d[2]		
RCR CSF														10/20d[2]				10/20d[2]		
MRI		10/20d	*				10/20d	*						10/20d[2]		X[8]	X	10/20d[2]		X[8]

P indicates Prior to Injections: P-1 wk is within 1 week prior the 1st dose; P is prior to the injections on the day of dosing.
ECG readings underlined above to be done in triplicate for subjects enrolled prior to protocol amendment D. Subjects enrolled after approval of amendment D will have triplicate ECG done only at Screen. All ECGs are sent for central reading.
DO1, DO2 and DO3 are drop-out visits; FU1, FU2, and FU3 are 4, 12, and 52 weeks after last dose of study treatment.
LP/CSF and MRI: the times are days after the visit (e.g., 10/20d is 10-20 days. Attempt to schedule MRI closer to 10 days than 20 days as the result must be received prior to the next dose).
RCR CSF: after aliquoting the required samples, any remaining CSF fluid from consenting subjects will be saved for RCR sample.
Visit window: +/- 7 days for dosing days; +/- 3 days for visits that are 1 week post-dose (see Section 5.1.2).
* The MRI result as determined by the central reader must be known before a subsequent dose can be given.

Table 2 Schedule of Assessments – Second Year (Cont.)

1. Any procedure or assessment marked may be done at an unscheduled visit as required.
2. LP performed in the morning (8 am−12 pm); MRI should not be done during the 3 days following an LP. The LPs at screening and Week 104 (FU1/104, FU1/DO 1 or 104 Ext) are mandatory. The LPs at 1 year and during the extension part of the study are optional. The final LP in the extension (FU1/208 or ext208/DO1) is highly encouraged.
3. LP/CSF for biomarkers and PK assays, plasma PK and matching serum samples: at screen, Wk 52 Wk FU1/104 (or FU1/DO 1 or Wk 104 Ext), Wk 156 and Wk FU1/208 (or ExtFU1/DO 1). See Section 5.2.14.2.
4. FCSRT-IR performed up to 1 month prior to screening can be used to satisfy inclusion criteria.
5. Women who are of childbearing potential must have a urine pregnancy test done at the site prior to each dose.
6. RCR plasma and RNA samples should be taken at the same time as the blood samples taken during the LP visit.
7. Subjects continuing directly into the Extension, should follow Week 104 Ext schedule in Table 3. FU2/112 and FU3/152 visit in Table 2 will not be performed.
8. The final MRI should be done approximately 4 weeks before the final follow-up visit to allow review before the final visit.
9. At screening, demographic data collected will include years of education.
10. During the screening period, Week 53, the Week 101 or DO1 and, Week 204, or Ext DO1 only, HbA1C, folic acid and, B12, T4, free T4, and thyroid stimulating hormone levels will also be assessed.
11. At FU, DO3, Ext FU3 or Ext DO3, only FAQ will be administered.
12. Optional follow-up/drop-out visit.

Table 3 Schedule of Assessments – Extension Year 1

Visit by week #	104 Ext	108	112	116	120	124	128	132	136	140	144	148	152
Dose Number	**27**	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**
Physical Exam			P										
Neurological Exam			P										
RCR Plasma and RNA	X[6]												
Vital Signs	P	P	P	P	P	P	P	P	P	P	P	P	P
ECG			P							P			
Blood and Urine Labs			X							X			
Urine Pregnancy Test[5]	P	P	P	P	P	P	P	P	P	P	P	P	P
PK plasma			P							P			
ADA samples			P							P			
Plasma Biomarkers													
CDR	P			P			P			P			
FAQ, NPI-Q, GDS	P						P						
MMSE	P			P			P			P			
Dementia Assessment	P						P						
ADAS-Cog	P			P			P			P			
FCSRT-IR	P			P						P			
CANTAB	P												
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X
LP/CSF, plasma PK and matching serum sample[3]	10/20d[2]												
RCR CSF	10/20d[2]												
MRI	10/20d	*					10/20d	*					10/20d

Also refer to footnotes Table 2.

Table 4 Schedule of Assessments – Extension Year 2

Visit by week #	156	160	164	168	172	176	180	184	188	192	196	200	204	FU1/ 208	FU2/ 216	FU3/ 256	Unsch.[1]	ExtFU1/ DO1	ExtFU2/ DO2	ExtFU3/ DO3[12]
Dose Number	40	41	42	43	44	45	46	47	48	49	50	51	52							
Physical Exam	P												P		X	X	X		X	X
Neurological Exam	P												P		X	X	X		X	X
RCR Plasma and RNA	X[6]													X[6]				X[6]		
Vital Signs	P	P	P	P	P	P	P	P	P	P	P	P	P	X	X	X	X	X	X	X
ECG				P						P			P		X		X		X	
Blood and Urine Labs				X						X			X[10]		**X**	X	**X**	X[10]	X	X
Urine Pregnancy Test[5]	P	P	P	P	P	P	P	P	P	P	P	P	P		X		X		X	
PK plasma				P						P			P		X		X		X	
ADA samples				P						P			P		X		X		X	
Plasma Biomarkers															X		X		X	
CDR	P			P			P			P				X		X	X	X		X
FAQ, NPI-Q, GDS	P						P							X		X[11]	X	X		X[11]
MMSE	P			P			P			P				X			X	X		
Dementia Assessment	P						P							X			X	X		
ADAS-Cog	P			P			P			P				X			X	X		
FCSRT-IR				P						P				X			X	X		
C-SSRS	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	X	X	
LP/CSF, plasma PK and matching serum sample[3]	10/20d[2]													10/20d[2]			X	10/20d[2]		
RCR CSF	10/20d[2]													10/20d[2]				10/20d[2]		
MRI	*					10/20d	*							10/20d[2]		X[8]	X	10/20d[2]		X[8]

Also refer to footnotes in Table 2.

Table 5 Schedule of Assessments – Open-Label Extension Year 1 - for ApoE ε4 carriers previously on: 1) Placebo, 2) 105 mg Gantenerumab and 3) 225 mg Gantenerumab meeting Criteria for Dose Reduction due to ARIAs

Visit by week #	OLE Pre-baseline (8 weeks)	Day 1 (OLE Baseline)	4	8	12	16	20	24	28	32	33	36	40	44	48	52
Dose Number		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**		**10**	**11**	**12**	**13**	**14**
Dose (mg)		**105**	**105**	**105**	**225**	**225**	**225**	**450**	**450**	**900**		**900**	**1200**	**1200**	**1200**	**1200**
Physical Exam		P						P								P
Neurological Exam		P						P								P
Vital Signs		P	P	P	P	P	P	P	P	P		P	P	P	P	P
ECG		P														P
Blood Labs		P														X
Urine Pregnancy Test[4]		P	P	P	P	P	P	P	P	P		P	P	P	P	P
PK plasma		P								P	X	P		P		
ADA samples		P								P		P				
CDR		P-1wk						P								P
FAQ		P-1wk						P								P
MMSE		P-1wk						P								P
Dementia Assessment		P-1wk						P								P
ADAS-Cog		P-1wk						P								P
FCSRT-IR		P-1wk						P								P
C-SSRS		P-1wk						X								X
MRI	X			X[2]	*		X[2]	*	X[2]	*		X[2]	*		X[2]	*

Refer to Table 8 footnotes.

Table 6 Schedule of Assessments – Open-Label Extension Year 1- for: 1) ApoE ε4 non-carriers and 2) ApoE ε4 Carriers receiving 225 mg Gantenerumab until the End of Double-blind Treatment

Visit by week #	OLE Pre-baseline (8 weeks)	Day 1 (OLE Baseline)	4	8	12	16	17	20	24	28	32	36	40	44	48	52
Dose Number		1	**2**	**3**	**4**	**5**		**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Dose (mg)		**225**	**225**	**450**	**450**	**900**		**900**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**	**1200**
Physical Exam		P							P							P
Neurological Exam		P							P							P
Vital Signs		P	P	P	P	P		P	P	P	P	P	P	P	P	P
ECG		P														P
Blood Labs		P														X
Urine Pregnancy Test[4]		P	P	P	P	P		P	P	P	P	P	P	P	P	P
PK plasma		P				P	X	P		P						
ADA samples		P				**P**				P						
CDR		P-1wk							P							P
FAQ		P-1wk							P							P
MMSE		P-1wk							P							P
Dementia Assessment		P-1wk							P							P
ADAS-Cog		P-1wk							P							P
FCSRT-IR		P-1wk							P							P
C-SSRS		P-1wk							X							X
MRI	X		X^2	*	X^2	*		X^2	*		X^2	*			X^2	*

Refer to Table 8 footnotes.

Table 7 Schedule of Assessments – Open-Label Extension Year 2 for all Participants

Visit by week #	56	60	64	68	72	76	80	84	88	92	96	100	101	104
Dose Number	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**25**	**26**		**27**
Physical Exam														P
Neurological Exam														P
Vital Signs	P	P	P	P	P	P	P	P	P	P	P	P		P
ECG														P
Blood Labs														X
Urine Pregnancy Test[4]	P	P	P	P	P	P	P	P	P	P	P	P		P
PK plasma			P									P	X	P
ADA samples			P											P
CDR						P								P
FAQ						P								P
MMSE						P								P
Dementia Assessment						P								P
ADAS-Cog						P								P
FCSRT-IR						P								P
C-SSRS						X								X
MRI					X[2]	*						X[2]		*

Refer to Table 8 footnotes.

Table 8 Schedule of Assessments – Open-Label Extension Year 3 for all Participants

Visit by week #	108	112	116	120	124	128	132	136	140	144	148	152	OLE156/ FU/DO [5]	Unsch.[1]
Dose Number	**28**	**29**	**30**	**31**	**32**	**33**	**34**	**35**	**36**	**37**	**38**	**39**		
Physical Exam													X	X
Neurological Exam													X	X
Vital Signs	P	P	P	P	P	P	P	P	P	P	P	P	X	X
ECG													X	X
Blood Labs													X	**X**
Urine Pregnancy Test[4]	P	P	P	P	P	P	P	P	P	P	P	P	X	X
PK plasma								P					X	X
ADA samples								P					X	X
CDR						P							X	X
FAQ						P							X	X
MMSE						P							X	X
Dementia Assessment						P							X	X
ADAS-Cog						P							X	X
FCSRT-IR						P							X	X
C-SSRS						X							X	X
MRI					X2	*						**X2,3**	*	X

Table 8 Schedule of Assessments – Open-Label Extension Year 3 for all Participants (Cont.)

Note: Visit window: +/- 7 days for dosing days; +/- 3 days for visits that are 1 week post-dose.

OLE = Open-Label Extension; P = prior to study drug administration: P-1 wk is within 1 week prior the first dose.

Eligibility for Part 3 should be confirmed during OLE pre-baseline, and MRI should be performed within 8 weeks and the results available before the first dosing visit in the OLE. Additional assessments can be performed as per the investigator's judgment.

MRI scans must be performed within a maximum of 20 days *(ideally 10–20 days)* after dose administration and results made available and reviewed before the next scheduled dose.

* The MRI result as determined by the central reader must be known before a subsequent dose can be given.

[1] *Any procedure or assessment may be performed at an unscheduled visit as required.*

[2] Subjects will be asked if they experience CNS adverse events up to 1 week before each MRI is performed.

[3] The results of the final MRI should be available before the final follow-up visit to allow review before the final visit *(after the last dose for patients not continuing in Part 3 extension after 3 years)*.

[4] Women who are of childbearing potential must have a urine pregnancy test done at the site prior to each dose.

[5] Follow-up/drop-out visit to be performed 4 weeks after the last dose during the initial 152 weeks of treatment.

Table 9 Schedule of Assessments – Open-Label Extension Years 4 and 5 for Participants Continuing Part 3 until July 2020

Visit by week #	*156*	*160–176*	*180*	*184–204*	*208*	*212–Onwards (Up to 236)*	*OLE/FU/DO* [5]	*Unsch.* [1]
Dose Number	*40*	*41–45*	*46*	*47–52*	*53*	*54–Onwards (Up to 60)*		
Physical Exam	P				P		X	X
Neurological Exam	P				P		X	X
Vital Signs	P	P	P	P	P	P	X	X
ECG	P				P		X	X
Blood Labs	P				P		X	X
Urine Pregnancy Test[4]	P	P	P	P	P	P	X	X
PK plasma	P				P		X	X
ADA samples	P				P		X	X
CDR	P							
FAQ	P							
MMSE	P		P		P		X	X
Dementia Assessment	P							
ADAS-Cog	P							
FCSRT-IR	P							
C-SSRS	P		P		P		X	X
MRI	*	L[2, 3]	*	L[2, 3]	*	L[2, 3]	*	X

Table 9 Schedule of Assessments – Open-Label Extension Years 4 and 5 for Participants Continuing Part 3 until July 2020 (Cont.)

Note: Visit window: +/- 7 days for dosing days.

L =an MRI after the Last dose within the indicated interval; OLE=Open-Label Extension; P =prior to study drug administration and prior to the injections on the day of dosing.

The schedule of assessment outlines the maximum number of week visits and doses until July 2020 and serves as guidance. The duration of Part 3 extension will vary for each subject dependent on when the subject begins the OLE.

MRI scans are scheduled at approximately 6-month intervals and is mandatory after the last study drug administration. The time between the previous scan and the final study scan should not exceed 8 months.

An MRI must be performed within 20 days (ideally 10–20 days) after dose administration and results made available and reviewed before the next scheduled dose.

** The MRI result as determined by the central reader must be known before a subsequent dosing visit and should be available before the OLE follow-up/drop-out visit to allow review before the final visit.*

[1] *Any procedure or assessment may be performed at an unscheduled visit as required.*

[2] *Subjects will be asked if they experience CNS adverse events up to 1 week before each MRI is performed.*

[3] *The results of the final MRI (after the last dose) should be available before the final follow-up visit to allow review before the final visit.*

[4.] *Women who are of childbearing potential must have a urine pregnancy test done at the site prior to each dose.*

[5] *OLE follow-up/drop-out visit to be performed 4 weeks after the last dose in Years 4or 5 of Part 3.*

5.1 General Instructions by Study Phase

All subjects must sign and date the most current IRB/IEC-approved written informed consent before any study specific assessments or procedures are performed. Recording of adverse events begins after the informed consent form is signed.

In general, results of study assessments should be shared with the subject only if the result may require that some action related to safety be taken. For example an abnormal MRI which means an unscheduled MRI will be done. This is to minimize any expectation bias.

See also Section 4.5 on concomitant medication use during the study.

5.1.1 Assessors for Clinical Scales and Order of Assessments

As much as feasible, the CDR should be administered for a single subject by the same assessor throughout the study and that assessor should not perform the MMSE or ADAS-Cog. However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR must be performed first. The CDR assessor must be involved in the dementia assessment (Section 5.2.8).

The remaining assessments may be done by other site staff as long as they have been qualified, trained, and where necessary certified to perform the scale. As much as possible for any one scale, the same assessor should be used throughout the study.

When done at the same visit, other than screening (see below) the order of the following cognitive assessments should be: CDR first (the entire scale in full), FCSRT before the ADAS-cog, ADAS-cog before the MMSE, and then CANTAB. The order should be FCSRT, ADAS-Cog, and then MMSE at visits where these are the only assessments. As they are informant based and not subject-based questionnaires, there is no restriction on the order of the FAQ and NPI-Q. As a general rule, the test sequence should remain the same for a given subject as at baseline and testing should occur around the same time of day at each visit.

5.1.2 Screening Period

The screening period is up to 8 weeks. The screening assessments are shown in the Schedule of Assessments in Table 1.

It is recommended that the first screening tests done are the CDR, FCSRT-IR, and MMSE in any order. If the subject doesn't qualify on the basis of these tests the subject may be re-screened again after at least 3 months have passed if recruitment for the study is still on-going (see inclusion criteria 13, 14, and 15).

As noted in exclusion criteria 20, 21, and 22, subjects may be re-screened after appropriate treatment if they were originally excluded for abnormal thyroid, B12, or HbA1C results.

Subjects can be re-screened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still on-going. In this case, all screening assessments must be repeated other than the LP/CSF testing if done previously for this study.

Subjects can be re-screened if there is a substantial change in the subject's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing.

Other laboratory tests which would exclude the subject may be repeated once (as unscheduled labs) if it is suspected that the abnormal result is transient and likely to be normal at repeat.

The remaining screening tests except the lumbar puncture and MRI (and PET scan if a PET substudy subject) should be done within 1–2 weeks of signing the informed consent (to allow adequate time for the remaining tests). As soon as all these results are available and none exclude the subject from the trial, the CSF collection and MRI scan should be done. If the subject has had a brain MRI within the last 6 months as part of the evaluation of cognitive impairment, and if the scan did not have any obvious findings that would exclude the subject from the study, the CSF results can be obtained before the screening MRI is done and the screening MRI should then be done only after it is known that the CSF results satisfy the selection criteria. If no recent scan is available, then the MRI should be done first and the lumbar puncture done after it is known the MRI satisfies the selection criteria unless, in the opinion of the Investigator there is sufficient reason that the LP should be done prior to the MRI.

It may take several days to receive the results of the MRI or CSF, and on occasion the originally scheduled MRI or CSF collection day may need to be postponed and in the case of the MRI, it may need to be repeated. Therefore the scheduling of these tests needs to be done carefully and should begin as soon as possible.

For subjects in the PET substudy, all other screening results including those on MRI and CSF will need to be available before the PET. In these cases the MRI appointment and LP should be scheduled to occur no more than 3 weeks after the beginning of the screening period. This is to allow sufficient time for the PET scan to be done and evaluated before the end of the screening period. In rare cases where an MRI needs to be repeated or any other unexpected delay due to logistical or technical reasons, this may necessitate extending the screening period by a few days. Extending the screening period beyond 8 weeks should be in exceptional circumstances only and careful scheduling should remain a priority.

A Subject Eligibility Checklist documenting the investigator's assessment of each screened subject with regard to the protocol's inclusion and exclusion criteria is to be completed by the investigator.

A screen failure log must be maintained by the investigator.

5.1.3 Treatment Period during Part 1 of the Study (Including Day of First Dose)

See Section 6.4 regarding treatment assignment.

All baseline assessments must be done before the first dose of study medication is given.

Subjects will receive up to 26 SC drug administrations over the course of 2 years in Part 1 of the study with a 4-week interval between each dose. On each dosing day, after all assessments indicated in the schedule of assessments to be done prior to dosing are completed, the gantenerumab or matching placebo will be administered SC at room temperature. For the first 4 doses, subjects should be observed for a minimum of 2 hours after dosing. For doses 5 and beyond, the subject may leave the study center soon after the injections if the subject appears to be tolerating the injections. Rescue medications/equipment to treat anaphylactic/anaphylactoid reactions must be available at the site. Subjects and study partners will be alerted to watch for signs of anaphylactic/anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

The schedule (Table 1, Table 2) shows visits after baseline by the number of weeks since the first dose. It also shows when assessments should be done relative to the time of the injections. Visits at which the subject receives study medication may take place within ±7 days of the exact date. Visits that occur one week after a dose may take place ± 3 days of the exact date. However all visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be done on the same day, but if necessary, assessments may be done over more than one day. Preferably, all clinical scales and CANTAB should be performed on the same day.

The investigator may choose to repeat the informed consent process if the subject has had appreciable cognitive decline during the study.

5.1.3.1 Procedures for New MRI Findings in Part 1 of the Study

In addition to any local reading as per local procedures and requirements, all MRIs will be reviewed by an expert central reader within approximately 1 week of receipt, and a report provided to the site. For the purposes of overall study relevant decisions and recommendations including patient eligibility as well as for analysis, results from the central expert read will be used. Any time the central reader identifies a new MRI finding, the study center medical staff and the sponsor will be rapidly notified. For relevant new MRI findings (as defined in the MRI-C Charter), the Sponsor will rapidly notify the MRI-C, who will then be actively involved in the review and can furthermore make recommendations that can deviate from the protocol guidelines, as deemed necessary. The iDMC will also be informed about relevant new MRI findings (see Section 10).

As described below, MRI findings will be classified into one of three types: ARIA-Edema (ARIA-E), ARIA-Hemosiderin (ARIA-H), and non-ARIA. If an MRI scan shows any new finding, the following action should be taken:

1. The site will contact the subject and study partner as soon as possible to determine if there are any symptoms that may be related to the MRI finding. If the subject has developed or develops symptoms, the subject should be seen before the next scheduled visit, and the symptoms should be reported in the electronic case report form (eCRF) (see Section *7.1.4*, MRI Observations).
2. A 4-week follow-up MRI will be done.

Prior to the follow-up MRI, the site should immediately inform the Sponsor if there are any new or worsening symptoms that may be related to the MRI findings.

5.1.3.1.1 New ARIA-E Findings in Part 1 of the Study

If the MRI shows new ARIA-E findings, the investigator will take action as described above. Treatment will be withheld and the subject will continue to attend the scheduled visits and will have a follow-up MRI approximately 4 weeks after the prior MRI. MRIs will then be done approximately every 4–8 weeks (done as "unscheduled" if not associated with the current visit schedule) until the ARIA-E finding has resolved or has clearly decreased and stabilized (as per the central read) at which point treatment may be restarted at half the original dose level. Treatment will still end at the time the final dose was originally scheduled to occur.

If treatment is restarted, the MRI schedule returns to the frequency done at entry into the study. That is, "reset" MRIs will be done after the second, fourth, sixth, ninth, etc., dose after dosing resumes. However, because an MRI is required after the Week 104 visit, in some cases a "reset" MRI is not required after the Week 96 or Week 104 visits. If a second ARIA-E finding occurs, treatment will be permanently discontinued.

If possible, an LP (additional to those already specified) should be done near the time of identification of an ARIA-E finding to aid in understanding the mechanism of these findings.

5.1.3.1.2 New ARIA-H Findings (Microbleeds or Areas of Leptomeningeal Hemosiderosis) in Part 1 of the Study

Approximately 20% of MCI subjects will have one or more microbleeds on a standard 1.5 Tesla T2* MRI [25]. Because microbleeds may develop spontaneously in prodromal AD subjects, it is reasonable to allow for the occurrence of occasional microbleeds without altering the treatment regimen. The following describes the management of dosing in cases of new ARIA-H.

1) If the cumulative number of new ARIA-H within the last 12 months is more than 4, treatment must be immediately discontinued. This is the case no matter what the dosing was over the prior 12-month period (e.g., full dose, half dose, dose held).

If the above is not met, dosing will be changed according to the following:

2) If on a full dose and the cumulative number of new ARIA-H within the last 12 months is more than 2, the dose will be halved.

3) If on a half dose, treatment will be discontinued if the cumulative number of new ARIA-H is more than 2 within the shorter of the last 12 months or since the dose was halved.

These limits apply for both 1.5T and 3T magnets.

After any new ARIA-H findings (microbleed or new area of leptomeningeal hemosiderosis), dosing can continue as long as the criteria for dose discontinuation is not met. However, the dose due after the 4 week follow-up MRI should not be given until

the MRI result is known. If criteria for dose alteration due to ARIA-H was not met, then no further action is needed after the 4 week follow-up MRI unless suggested by the MRI-C.

5.1.3.1.3 New Non-ARIA MRI Findings in Part 1 of the Study

In the case of new non-ARIA MRI findings (e.g., cases of ischemia, cerebral infarction, or other lesions) the MRI-C may propose further actions, if deemed appropriate (e.g., dose modification, additional MRI sequences, or recommendations for additional testing for diagnostic purposes).

5.1.4 Part 2 - Extension Period for Continued Double-Blind Treatment

Subjects who complete Part 1 of the study, up to and including the Week 104 visit, may continue to receive double-blind study medication during the optional Part 2 of the study after signing informed consent for the additional treatment.

Subjects may receive up to 26 additional SC administrations of their originally randomized study drug over the course of 2 years with a 4-week interval between each dose. On each dosing day, after all assessments indicated in the schedule of assessments to be done prior to dosing are completed, the gantenerumab or matching placebo will be administered SC at room temperature.

The schedule Table 3 and Table 4) shows visits during Part 2 of the study by the number of weeks since the first dose. It also shows when assessments should be done relative to the time of the injections. Visits at which the subject receives study medication may take place within ±7 days of the exact date. However, all visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be done on the same day, but if necessary, assessments may be done over more than 1 day. Preferably, all clinical scales should be performed on the same day.

As noted in Section 5.1.4.3 below, dosing at certain visits during the extension may not require the subject to come to the study center.

The investigator may choose to repeat the informed consent process if the subject has had appreciable cognitive decline during the study.

5.1.4.1 Procedures to Follow for Subjects who reach the Week 104 Visit prior to Approval of Amendment D

If a subject completes the Week 104 visit prior to approval of protocol amendment D, the subject may still continue in the optional Part 2 of the study once approval is received.

If Week 104 has been completed, and approval of amendment D is received prior to Week 112, the subject can be assessed and dosed as for the appropriate week (Week 108 or 112) in Table 3. In this case, the original visit schedule relative to baseline will be maintained as if the subject had not missed a dose and/or visit, as the case applies.

If amendment D approval is not received by the time the subject completes the follow-up Week 112 visit in the main study, the subject may still receive extended treatment once approval is received. In this case, the original visit schedule relative to baseline will be

maintained as if they had not missed a dose and/or visit, as the case applies. However, the assessments for Week 104Ext must be performed with the exceptions of RCR plasma and RNA, LP/CSF (with plasma PK and matching serum sample), RCR CSF, CANTAB, and MRI (which were already performed at Week 104/FU1 visit.

5.1.4.2 Procedures to Follow for Subjects who reach the Week 104 or 112 Visit without having made a Decision to Continue in Part 2 of the Study

If the amendment has been approved and the decision to continue double-blind treatment is not taken at Week 104, the schedule in Table 1 should be followed. If the decision is not made by the time of the Week 112 visit, the subject should have the final visit and must be discontinued from the study.

5.1.4.3 Dosing during Part 2 of the Study

For sites and subjects where this is practical, visits that require only dosing, vital signs and C-SSRS assessments may be done at the subject's residence conducted by appropriate site staff.

5.1.4.4 Procedures for new MRI findings in Part 2 of the Study

The procedures are the same as for Part 1 except for the following:

The MRI-C is not required to review new MRI findings that are typical of ARIA. The MRI-C will review findings where any of the following apply:

- The finding is not a typical ARIA finding (e.g., ischemic lesion)
- The subject has one or more new CNS adverse events which the investigator assesses as possibly related to the MRI finding
- Review by the Committee is requested by the central reading center, investigator, Sponsor, or iDMC

5.1.5 Treatment-Free Follow-up

Subjects are considered to be on treatment until 4 weeks after the last dose. All subjects (including premature withdrawals) will be followed for 12 weeks and, optionally, 1 year (52 weeks) after the last dose. These assessments (see Table 2 and Table 4 - FU1/DO1, FU2/DO2, and FU3/DO3 visits) should also be done if possible in case a subject prematurely withdraws consent for the study or is withdrawn early for other reasons. FU3/DO3 visit is optional for subjects who do not continue in the open-label extension and not needed for those entering Part 3, as all relevant assessments will be performed during Part 3 prebaseline and baseline (Table 5 and Table 6). For subjects continuing in Part 3, treatment–free follow-up is estimated to last approximately between 12 and 18 months, depending on the approval of study protocol WN25203G by local Competent Authorities (CAs). During this period, unscheduled assessments may be performed at any time.

5.1.6 Part 3 – the Open-Label Extension

Subjects who received double-blind treatment and had at least one follow-up/drop-out visit will be eligible to enter Part 3 after signing an informed consent for the additional treatment with higher doses of gantenerumab. Subjects who meet any of the criteria

outlined in Section 4.4 will not be eligible for Part 3. Eligibility for Part 3 should be confirmed within 8 weeks prior to the first dose administered (see Table 5 and Table 6).

APOE ε4 status will be communicated to subjects, and appropriate counseling will be offered.

Subjects may receive up to 39 SC administrations over the course of the 3-year open-label extension with a 4-week interval between each dose. *All subjects who complete 3 years of open-label treatment will be given the option of extending open-label treatment beyond the initial 3 years until July 2020 and may receive up to 21 additional administrations every 4 weeks during Years 4 and 5 (up to a maximum of an additional 19 months). The final number of SC administrations will depend on when a subject enters Part 3 and receives the first dose of open-label gantenerumab.*

On each dosing day, after all scheduled assessments to be done prior to dosing are completed, gantenerumab will be administered SC at room temperature. *For the first 4 doses, subjects should be observed for a minimum of 2 hours after dosing. For doses 5 and beyond, subjects should be observed for a minimum of 1 hour after dosing (if the subject appears to be tolerating the injections). Rescue medications and equipment to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for home nursing visits. Subjects and study partners will be alerted to watch for signs of anaphylactic/anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.*

The schedule of assessments in Part 3 (Table 5, Table 6, Table 7, *Table 8, and Table 9*) displays when assessments should be done relative to the time of gantenerumab administration. It includes separate schedules for Year 1 for APOE ε4 carriers previously on placebo and 105 mg gantenerumab (Table 5) and for APOE ε4 carriers previously on 225 mg gantenerumab and for the non-carriers (Table 6). All visits should be scheduled relative to the first dosing visit ("Day 1- baseline") in the open-label extension, as close as possible to the exact day. As in the Parts 1 and 2, all visits on which the subject receives study medication may take place within 7 days of the scheduled date. It is preferred that all assessments for a visit are performed on the same day, but if necessary, assessments may be done over more than 1 day. Preferably, all clinical scales should be performed on the same day. For the PK analysis, it is important to capture date and time of dosing and PK sampling correctly. *In Part 3 for certain dosing visits, the subject may not be required to return to the study center. At select sites and specified visits, study drug administration and limited safety assessments may be performed by home nursing staff.*

The investigator may choose to repeat the informed consent process if the subject has had appreciable cognitive decline during the study.

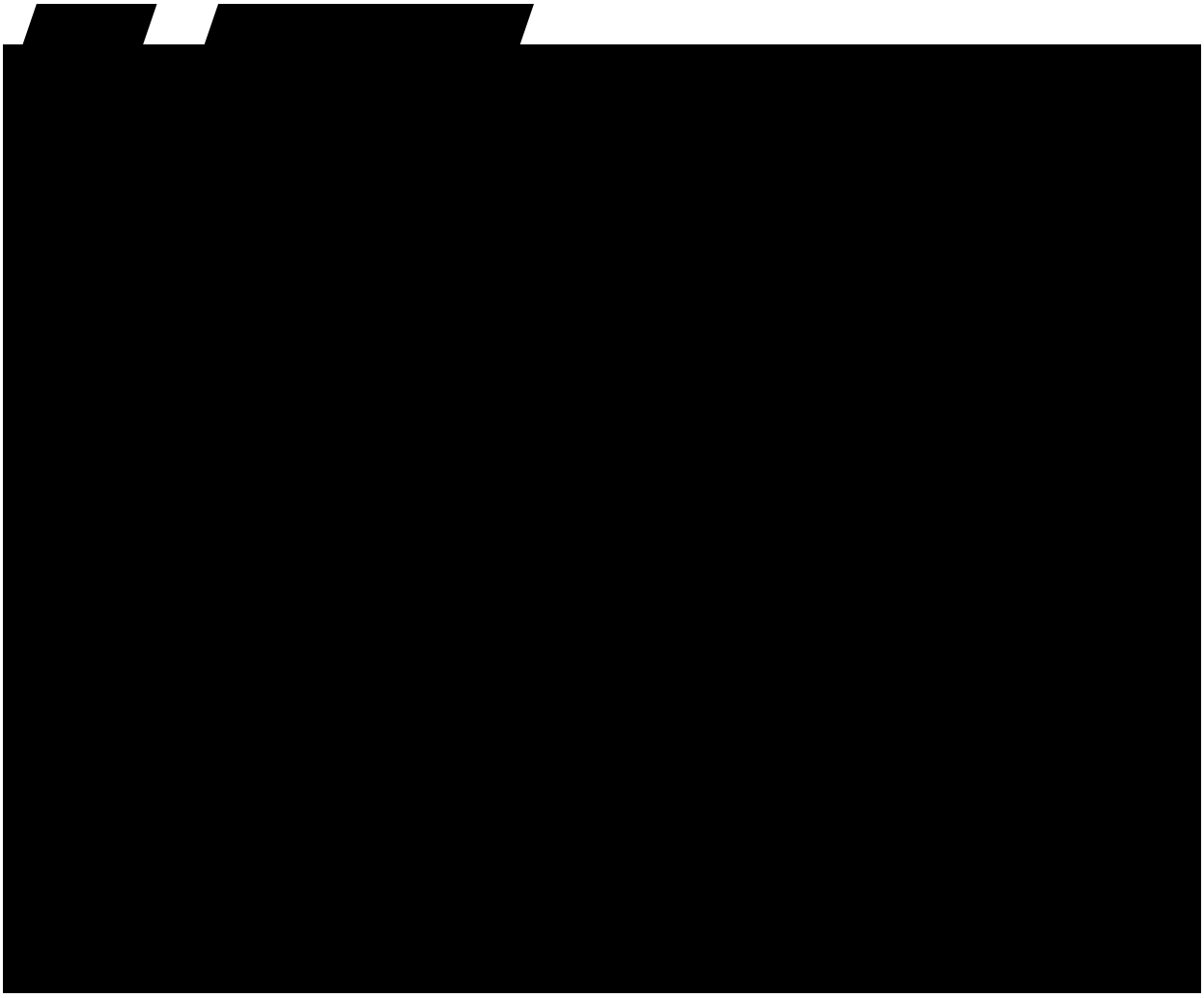
5.1.6.1 Procedures for new MRI findings in Part 3 of the Study

MRI scans in Part 3 will be performed according to the schedule of assessments, prior to each increase in gantenerumab dose (Table 5 and Table 6) and then at regular intervals *thereafter* (Table 7, Table 8, *and Table 9*).

All MRI scans will be read and reported by the central MRI reader in alignment with the processes from Parts 1 and 2 of the trial. When the central reader identifies a new MRI finding, the study center medical staff and the Sponsor will be notified, and in the case of relevant new MRI findings (as defined in the MRI-C Charter), the Sponsor, in turn, notifies the MRI-C concurrently. The MRI-C is actively involved in review and has the remit to make recommendations that may deviate from the protocol guidelines, as deemed necessary.

MRI findings are classified as ARIA-E, ARIA-H, and non-ARIA. Information about potential symptoms will be collected prospectively (i.e., the site will contact the subjects up to 1 week before each MRI to ask if they experience CNS adverse events, as described in Section *7.1.4*).

Management of MRI findings are presented in sections below.



5.1.6.1.3 New Non-ARIA MRI Findings

The MRI-C may be alerted in cases of new non-ARIA MRI findings (e.g., cases of hematoma, large cerebral infarction, or other lesions), if the central reader or sponsor requests the committee to review the MRI.

5.2 Assessments and Procedures

5.2.1 CDR

The CDR is used to characterize six domains of cognitive and functional performance applicable to Alzheimer disease and related dementias: Memory, Orientation, Judgment & Problem Solving, Community Affairs, Home & Hobbies, and Personal Care. The necessary information to make each rating is obtained through a semi-structured interview of the subject and a reliable informant or collateral source (e.g., family member). Details of the CDR can be found at the website: *http://www.biostat.wustl.edu/~adrc/cdrpgm/index.html. The scale will not be administered beyond the initial 3 years of Part 3.*

5.2.2 Functional Activities Questionnaire (FAQ)

The FAQ [26] is an informant-based assessment which presents a forced choice of 4 levels of functioning for 10 activities of daily living (ADL). *The scale will not be administered beyond the initial 3 years of Part 3.*

5.2.3 MMSE

The MMSE consists of a set of standardized questions to assess a subject's mental status and identifies the individual's general level of impairment [27]. The questions target 5 areas; orientation, short term memory retention, attention, short term recall and language. *The MMSE is the only scale that will be collected beyond the initial 3 years of Part 3.*

5.2.4 Neuropsychiatric Inventory (NPI-Q)

The NPI-Q [28] was developed to assess a wide range of behaviors encountered in dementia patients, to provide a means of distinguishing severity of behavioral changes,

and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 10 behavioral domains are evaluated on a 3-point scale (mild, moderate, and severe). The caregiver distress portion of the scale will not be used in this study. The scale will not be administered during Part 3.

5.2.5 Alzheimer Disease Assessment Scale-Cognition (ADAS-Cog)

The modified version will be used which has 13 items. The modified items are: addition of delayed word recall and number cancellation and use of only one trial for word recognition. This is the version used in the ADNI protocol (http://www.adni-info.org/Scientists/ADNIGrant/ADNIProtocol.aspx). Equivalent alternate forms of the word recall and word recognition and number cancellation subtests will be used in successive test administrations. *The scale will not be administered beyond the initial 3 years of Part 3.*

5.2.6 Free and Cued Selective Reminding Test (FCSRT-IR)

The version of FCSRT-IR to be used will use written words and immediate recall after each card with four words is completed [29]. The FCSRT-IR is a measure of memory under conditions that control attention and cognitive processing in order to obtain an assessment of memory unconfounded by normal age related changes in cognition. FCSRT-IR performance has been associated with preclinical and early dementia in several longitudinal epidemiological studies [30]. *The scale will not be administered beyond the initial 3 years of Part 3.*

5.2.7 Cambridge Neuropsychological Test Automated Battery

The CANTAB is a computerized assessment battery consisting of tests for neuropsychological function. Details of CANTAB can be found at: www.cantab.com/camcog/default.asp. The tests selected for this study are listed in 8.1.2.1 and additional information on the CANTAB can be found in Appendix 2. The scale is administered during the first 2 years of double-blind treatment only.

5.2.8 Dementia Assessment

This is to assess if the subject has progressed to a diagnosis of dementia. It should involve the assessor who completes the CDR and is done during the visit after reviewing the results of all scales done at that visit. It is done even if the subject was judged to have dementia at a prior assessment. In most cases, to meet criteria for dementia, worsening from baseline should be seen on one or more domains of the CDR, the FAQ and on cognition (as assessed by ADAS, MMSE, and during the first 2 years of treatment by CANTAB). If dementia is judged to be present, an additional determination will be made as to whether it is considered to be dementia of the Alzheimer's type. *Dementia assessment will not be performed beyond the initial 3 years of Part 3.*

5.2.9 Modified Hachinski Ischemia Scale

This is a simple clinical tool currently used for helping to differentiate different types of dementia (primary degenerative, vascular or multi-infarct, mixed type).

5.2.10 MRI

The MRI should be performed using a 1.5 Tesla magnet. In exceptional circumstances if a 1.5 T magnet is not available in reasonable proximity to the study center, a 3 T magnet may be used.

MRI will be conducted for subject screening, for safety monitoring and to determine potential treatment effects on brain volume according to the Schedule of Assessments. The screening MRI will be used to help in determining whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions, etc.). MRI will be used during the course of this study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or vasogenic edema. Additional unscheduled MRIs may be utilized to better understand relevant CNS-related AEs (such as increased confusion) or to follow a sign which emerged at a scheduled scan; contrast agent may be used in such a case of follow-up if administration of contrast agent is considered safe for the subject according to local standards. MRIs done at screening, after the 12th and 26th dose in Part 1 of the study, and after the 39th and 52nd dose in Part 2, will be used for volumetric analysis. In Part 3, MRIs performed before the first dose, after 13th, 26th, and 39th dose will be used for volumetric analysis. The following MRI sequences will be acquired every time an MRI is scheduled:

- 3D T1 - weighted gradient echo scans
- T2* - weighted gradient echo scans
- T2 - weighted spin echo scans
- T2 - weighted Fluid attenuated inversion recovery (FLAIR) scans
- Diffusion weighted scans, if available

The MRI will take approximately 30 minutes to complete.

MRI should not be done unless at least 3 days have passed since a lumbar puncture. Further instructions regarding the MRI can be found in the separate MRI Manual. Scans will be reviewed by a central MRI Core Lab and it will be the assessment of the data as done by the central reader that will be used in the analysis.

5.2.10.1 Healthy Volunteer MRI Scans for Site Qualification

MRI acquisition of phantoms provides some information regarding how the proposed sequences are standardized at a site as well as the resultant quality of scans. However, this data is often not suitable enough to provide clarity on important aspects of the image quality for quantitative analysis of brain atrophy. Such issues include tissue contrast, susceptibility artifacts, and the effects of motion on the quality of scans. Thus as part of site qualification, 1 or 2 volunteers at each site should be recruited and scanned using the same machine and the same sequences to be used for the study before any subject is scanned in this study. These volunteers must not have any contraindications for MRI scanning (evaluation as per local procedures at the imaging site), and they will not be enrolled in the study nor undergo any other assessments as part of the trial. If volunteer scans are acquired, then they will be reviewed for suitable image quality and used for qualitative comparison with scans acquired after certain events as follows: Upon a major upgrade to the site's scanner, 4 months without any subject scans occurring at a site, or

any other event deemed significant enough to affect image quality, additional scans with the same volunteer should be acquired. This procedure will help ensure consistency in scanning quality over the duration of the study. Two volunteers are ideal in case one volunteer is no longer readily available for test scanning.

5.2.11 Pharmacokinetic [PK] Sampling

5.2.11.1 Plasma Gantenerumab

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the Schedule of Assessments Table 1, Table 2, Table 3, and Table 4 in Parts 1 and 2.

Samples from patients receiving placebo will not be assessed in the first instance, but retained for subsequent analysis if appropriate.

In Part 3, the PK sampling schedule follows the separate titration schedules for the APOE ε4 carriers and non-carriers during the first year (Table 5 and Table 6). Collection of plasma samples for pharmacokinetics during Years 2 and 3 of Part 3 for all participants is outlined in Table 7 and Table 8, respectively. *The PK sampling schedule during Years 4 and 5 is outlined in Table 9.*

Unused sample material may also be used for the purposes of current gantenerumab assay improvement.

5.2.11.2 CSF Gantenerumab (Parts 1 and 2)

An aliquot of CSF collected by lumbar puncture as detailed in section 5.2.14.2 (Table 1, Table 2, Table 3, and Table 4) will be allocated for the measurement of gantenerumab concentration.

Samples from patients receiving placebo will not be assessed in the first instance, but retained for subsequent analysis if appropriate.

Unused sample material may also be used for the purposes of current gantenerumab assay improvement.

5.2.12 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all subjects as noted in the Schedule of Assessments Table 1, Table 2, Table 3, and Table 4.

The procedures for the collection, handling and shipping of PK and ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site by the Sponsor. The total volume of blood taken for PK and ADA assessments will be approximately 85 mL in Part 1 of the study and approximately 12 mL each year that the subject continues in Part 2.

In Part 1 of the study, analysis of samples will be limited initially to those collected at the Baseline (pre-dose), Dose 6 (Week 20) and Follow-up (Week 112) occasions. For subjects participating in Part 2, sample analysis will be limited initially to Baseline

(pre-dose), Dose 6 (Week 20), Dose 29 (Week 112), Dose 43 (Week 168), Dose 52 (Week 204) and FU2 (Week 216).

For subjects participating in Part 3, blood samples for ADA will be collected during the first year as indicated in Table 5 for the APOE ε4 carriers and Table 6 for the non-APOE ε4 carriers. Collection of blood samples for ADA during Years 2 and 3 of Part 3 for all participants is outlined in Table 7 and Table 8, respectively. *Collection of blood samples for ADA during Years 4 and 5 of Part 3 for all participants is outlined in Table 9*. The analysis of the remaining samples for Parts 1, 2, and 3 of the study may be requested for some individuals as appropriate, dependent on the initial results.

Unused sample material may also be used for the purposes of current ADA assay improvement.

5.2.13 Clinical Genotyping

During screening, a mandatory 3 mL whole blood sample will be taken for DNA extraction from every subject who has consented to participate in the study. All subjects will be evaluated for ApoE ε4 status and Fcγ receptor genotype. Subjects will be assigned to study treatment based on ApoE ε4 status. Fcγ receptor genotype may play a role in PK and PD variability of antibody-based therapeutics and predict response/non response. ApoE ε4 status and Fcγ receptor genotype information will not be shared with the Investigator or the subject until the study is unblinded unless required by the relevant health authority or EC/IRB. Data arising from these analyses will be subject to the same confidentiality as the rest of the study. The procedures for the collection, handling and shipping of Clinical Genotyping samples are specified in the Laboratory Manual.

The APOE ε4 genotype information will be communicated to subjects continuing in the open-label extension (Part 3), and appropriate counseling will be offered.

5.2.14 CSF and Plasma Biomarker Sampling (Parts 1 and 2)

Samples will be collected from all subjects and will be used for research purposes to identify dynamic biomarkers that may be predictive of response to treatment with gantenerumab (in terms of dose, safety and tolerability) and will help to better understand the pathogenesis, course and outcome of Alzheimer's Disease and related diseases.

5.2.14.1 Plasma Biomarkers Sampling

Approximately 5 mL blood sample for biomarker analysis will be collected according to the Schedule of Assessments Table 1, Table 2, Table 3, and Table 4. A total of 45–60 mL of plasma will be collected throughout the course of the study (30–35 mL in Part 1 and an additional 15 mL in Part 2). These samples will be used for analysis of markers of amyloid deposition and clearance (e.g., $A\beta_{1\text{-}40}$ and $A\beta_{1\text{-}42}$, potentially β-amyloid pyroglutamate). The procedures for collection, handling and shipping of plasma biomarker samples are specified in the Sample Handling and Logistics Manual.

5.2.14.2 CSF Sampling

CSF samples will be collected according to the Schedule of Assessments Table 1, Table 2, Table 3, and Table 4. The lumbar puncture will be performed by an individual

who meets all local requirements and is proficient in the procedure. Post lumbar puncture care will be done in accordance with local practice.

CSF sampling will be done in the morning (between 8 AM and noon) to minimize potential diurnal variation of CSF parameters [31]. CSF and, in addition, matching blood samples (serum and plasma) will be taken at screening and Weeks 52, 104 (FU1 or 104Ext), 156, 208/FU1, and/or drop-out visits (as applicable). Serum samples may be used if required to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. Plasma samples will be collected for pharmacokinetics. Procedures for the processing of the CSF samples can be found in the Sample Handling and Logistics Manual.

Approximately 12 mL of CSF will be collected at each timepoint. The sample will be aliquoted on-site and used for:

- Local lab testing for cell count (erythrocytes and leukocytes with differential)
- Measuring the CSF gantenerumab levels (see Section 5.2.11.2), and biomarker analysis including $A\beta_{1-42}$, T-tau and P-tau, tentatively $A\beta_{1-40,}$ and markers of inflammation. This sample may also be used to support the development of biomarker assays for patient selection/stratification (i.e., Aβ, tau, P-tau).

Normal ranges for CSF cell counts will be sent to the sponsor by the site for data entry.

Unused CSF sample (up to 6 mL) will be kept for future Biomarker Research if the subject gives consent to RCR (see RCR CSF, below). The procedures for handling and shipping of CSF samples for biomarker analyses are specified in the Sample Collection, Handling and Logistics Manual.

5.2.15 Roche Clinical Repository Specimen(s)

Specimens for dynamic (non-inherited) biomarker discovery and validation will be collected from consenting subjects in Parts 1 and 2.

These specimens will be used for research purposes to identify dynamic biomarkers that are predictive of response to gantenerumab treatment (in terms of dose, safety, and tolerability) and will help to better understand the pathogenesis, course and outcome of Alzheimer's Disease and related diseases. They may also be used to support the development of biomarker and diagnostic assays.

Three types of specimens will be collected: RCR CSF (samples remaining from the CSF analysis described in Section 5.2.14.2 above) RCR plasma, and RCR RNA.

Analysis of plasma and CSF samples may include determination of markers of amyloid deposition and/or clearance, oxidative stress, neurodegeneration, inflammation, and other processes implicated in the pathogenesis of AD. RNA samples may be tested using techniques such as high-density microarray profiling and/or quantitative RT-PCR to study the expression profile of genes known to be involved in AD, and any other differentially expressed genes relative to treatment or dose response.

Specimens for dynamic biomarker discovery will be single coded like any other clinical sample (labeled and tracked using the subject's study identification number (see Section 17).

Specimens for genetic (inherited) biomarker discovery and validation will also be collected from consenting subjects (RCR DNA). Theses samples may be used to explore the associations of variants of genes implicated in susceptibility and pathogenesis of AD, such as Clusterin and PICALM, and therapy response or adverse events.

The pharmacogenetic information gathered through the analysis of specimens in the RCR is hoped to improve subject outcome by predicting which subjects are more likely to respond to specific drug therapies, predicting which subjects are susceptible to developing adverse side effects and/or predicting which subjects are likely to progress to more severe disease states. Such genetic samples collected for analysis of heritable DNA variations will be double coded: a new independent code will be added to the first code to increase confidentiality and data protection (see Section 17).

The results of specimen analysis from the RCR will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for subjects in the future.

All RCR specimens will be destroyed no later than 15 years after the final lock of the respective clinical database unless regulatory authorities require that specimens be maintained for a longer period. The specimens in the RCR will be made available for future biomarker research towards further understanding of treatment with gantenerumab, of Alzheimer's Disease, related diseases and adverse events and for the development of potential associated diagnostic assays. The implementation and use of the RCR specimens is governed by the Roche Clinical Repository policy to ensure the appropriate use of the RCR specimens.

5.2.15.1 Specimen Types [the following list is not exhaustive]

Plasma assays

Blood (one approximately 6.0 mL sample in EDTA) for plasma isolation will be obtained at various time points as shown in Table 1, Table 2, Table 3, and Table 4**.** For sampling procedures, storage conditions and shipment instructions see study Sample Handling and Logistics Manual.

Blood Sample for RNA Expression Profiling

Blood for RNA isolation (two 2.5 mL samples collected in PAXgene vacutainers) will be collected from consenting patients at various time points according to the Schedule of Assessments Table 1, Table 2, Table 3, and Table 4. Date of consent and specimen collection should be recorded on the associated RCR page of the eCRF. For sampling procedures, storage conditions and shipment instructions see study Sample Handling and Logistics Manual.

Blood sample for genetic analysis (RCR DNA)

Blood (approximately 6 mL in K3 EDTA) for DNA isolation will be collected as shown in Table 1. If, however, the RCR genetic blood sample is not collected during the scheduled visit, it may be collected at any time (after randomization) during the conduct of the clinical study. See study Sample Handling and Logistics Manual for more details.

5.2.16 Safety

5.2.16.1 Physical Examination

A general physical examination will be carried out at the time points listed in the Schedule of Assessments (for Part 3, please refer to Table 5, Table 6, Table 7, *Table 8, and Table 9*). Weight and height measurements will be done as part of the screening physical exam.

5.2.16.2 Neurological Examination

A neurological examination will be performed at time points listed in the Schedule of Assessments (for Part 3, please refer to Table 5, Table 6, Table 7, *Table 8, and Table 9*).

5.2.16.3 GDS

The Geriatric Depression Scale (short form) [32] is a self-report scale designed to identify symptoms of depression in the elderly. The scale consists of 15 questions which are answered yes or no on the basis of how the subject felt over the past week. Total scores of 0–5 are considered normal and scores of 6–15 are considered depressed. The scale will not be administered in Part 3.

5.2.16.4 Vital Signs

Vital signs (systolic and diastolic blood pressure and pulse rate) will be measured after the subjects have been in a supine position for at least 5 minutes at time points listed in the Schedule of Assessments (for Part 3, please refer to Table 5, Table 6, Table 7, *Table 8, and Table 9*).

5.2.16.5 ECG

After 5 minutes in a supine position, 12-lead ECG single read will be performed at the time points indicated in the Schedule of Assessments (for Part 3, please refer to Table 5, Table 6, Table 7, *Table 8, and Table 9*). Triplicate ECGs will be recorded at certain visits as indicated in the Schedule of Assessments during Parts 1 and 2 only. Triplicates should be done 2–5 minutes apart (i.e., 3 readings within 10 minutes). All ECGs will be recorded/digitized using a validated device. All ECGs will be read by the central reader. The investigator or designee must review the outputs to ensure there are no clear alerts for quality or clinical issues and then sign, and date the outputs.

5.2.16.6 Laboratory Assessments

Blood Chemistry: AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN/urea and serum creatinine (and creatinine clearance calculated by central lab). During the screening period, Week 53, Week 101 or DO1 in Part 1, Week 204, or Ext DO1 in Part 2, and at all visits with scheduled blood chemistry in Part 3, HbA1C, folic acid, B12, thyroxine (T4), free T4, and thyroid-stimulating hormone levels will also be assessed.

Hematology: hemoglobin, hematocrit, red blood cell (with morphology), white blood cell, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

Coagulation: prothrombin time (PT)

Urine for Drugs of Abuse: at screening only, urine samples will be analyzed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify subject eligibility pertaining to drug abuse.

Urinalysis: performed during Parts 1 and 2 only at the site by dipstick for blood, protein, glucose and pH. Microscopic examination will be performed by the central lab if blood and/or protein results are positive or strong positive.

Urinalysis for Pregnancy: urine pregnancy testing will be performed at the site for women of childbearing potential, and at the site for any other female participants if required by local regulations. Women who are of child-bearing potential must have a pregnancy test conducted at the site prior to each dose.

The total volume of blood taken for laboratory assessments will be approximately 130 to 215 mL over the course of Part 1 of the study and an additional 30–40 mL during each year of Part 2. During Part 3, the total volume of blood taken at scheduled visits will be approximately 111 mL *during the initial 3 years, and up 40 mL during Years 4 and 5*.

The procedures for the collection, handling and shipping of laboratory samples are specified in the manual provided by the central laboratory.

5.2.16.7 Columbia-Suicide Severity Rating Scale (C-SSRS)

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a subject (C-SSRS baseline) as well as any new instances of suicidality (C-SSRS since last visit). The structured interview prompts recollection of suicidal ideation, including the intensity of the ideation, behavior and attempts with actual/potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since last visit will be collected at subsequent visits during Parts 1 and 2.

The C-SSRS will be done at visits indicated in the Schedule of Assessments (for Part 3, please refer to Table 5, Table 6, Table 7, *Table 8, and Table 9*). It will be completed by the clinician after interviewing the subject and also the study partner when in attendance at the visit.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Formulation, Packaging and Labeling

A [redacted] antibody-producing cell line was established [redacted] by fermentation of a recombinant [redacted] cell line and subsequent purification of the antibody. [redacted]

The study drug must be stored according to the details on the product label. RO4909832 Drug Product should be stored at 2–8°C and protected from light. Study drug packaging will be overseen by the Roche clinical trial supplies department and will bear labeling with identification required by law, the protocol number, drug identification, and dosage.

The packaging and labeling of the study medication will be in accordance with Roche standard and local regulations.

Upon arrival of investigational products at the site, site personnel should check them for damage and verify proper identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to the monitor upon discovery.

6.2 Dose and Schedule of IMP

For details on dosing schedule see Sections 5.1.2, 5.1.4, and 5.1.6.

6.2.1 Dose Modifications, Interruptions, and Delays

Strict adherence to the planned dose regimen is required. However, a single missed dose may not automatically result in study withdrawal. If cognitive assessments were to have been done at a missed visit, these may be rescheduled to the next visit.

For details on dose modification due to MRI findings see Section 5.1.3.1.

6.3 Preparation and Administration of the IMP

6.3.1 Preparation and Administration of the IMP in Parts 1 and 2

Prior to administration, each vial of test drug or placebo needs to be reconstituted with [redacted] Water for Injection using a sterile needle and syringe. [redacted]

DO NOT SHAKE AND DO NOT FREEZE VIAL CONTENTS.

[redacted] Vials will contain either gantenerumab or placebo depending on the dose to be delivered. [redacted]

If reconstitution of the product has taken place in controlled and aseptic conditions (including the use of a laminar flow hood), the solution can be stored for up to 24 hours

at 2°C–8°C and 6 hours at ambient temperature. Otherwise, the product should be used immediately (within 2 hours) after reconstitution.

The study medication will be administered as [redacted] SC injections in the abdominal area. The SC injections are to be administered slowly [redacted]

Exposure of the study medication to direct sunlight in the vial or syringe should be avoided.

Parenteral Drug Products should be inspected visually for particulates prior to administration. Partially used vials should NOT be re-used.

Other parenterally administered medications should not be mixed with the study drug.

Personnel involved in reconstitution of and filling syringes with study medication must not be involved with subject care in the study nor communicate any observations made during the study drug preparation to any personnel involved in the care of the subject. Personnel who reconstitute and/or fill syringes may also give the injections but must observe the rules above for those involved in study drug preparation.

6.3.2 Preparation and Administration of the IMP in Part 3

Gantenerumab will be available in 2 drug product formulations during Part 3: [redacted], containing 105 or 225 mg gantenerumab ready for SC administration [redacted].

Gantenerumab doses of 105 and 225 mg will be administered SC [redacted] The 1200-mg gantenerumab dose will be administered SC [redacted]

All formulations should be stored at 2°C–8°C and protected from light. The liquid formulation in [redacted] can be stored for up to 6 hours at ambient temperature. If withdrawal from the vial (for the liquid formulation in vial) has taken place in controlled and aseptic conditions (including the use of a laminar flow hood), the solution can be stored for up to 24 hours at 2°C–8°C and 4 hours at ambient temperature once prepared; otherwise, the product should be used immediately after withdrawal from the vial. All drug product solutions should be brought to room temperature prior to administration to minimize discomfort during the injection.

6.4 Randomization, Blinding, and Unblinding

Randomization will be performed centrally using an interactive system (IxRS). After being screened, those subjects who meet all eligibility criteria will be randomly assigned, within each ApoE ε4 genotype group (i.e., 0ε4, 1ε4, 2ε4), to one of three treatment groups (gantenerumab 105 mg, gantenerumab 225 mg, or placebo). The ratio will be

2 active to 1 placebo. Within the 2ε4 genotype all subjects receiving gantenerumab will receive 105 mg. Based on the ADNI data, it is expected that for the 0ε4 and 1ε4 genotypes receiving gantenerumab, approximately 40% will receive 105 mg and 60% will receive 225 mg. Except in circumstances where a health authority, EC or IRB requires the subject be told of his/her ApoE genotype, the individual patient ApoE genotype results will be blinded to the subjects, investigators, and the Sponsor, and will be supplied directly to the IxRS vendor by the testing lab so that the information can be incorporated at the time of randomization.

Randomization to treatment allocation will also be stratified by geographical region of the study center.

Subjects participating in the PET substudy will also be allocated to a study treatment as described above to achieve the ratio 2 active to 1 placebo.

The study is conducted in a double-blind manner in order to minimize potential bias from investigators and subjects. Except as described in Section 10, the Sponsor will be blinded to the study treatments (randomized and actually given). Treatment allocation for patients who continue in the optional Part 2 of the study will continue to be double-blinded.

The Master Randomization or Master Medication list will not be available at the study center, to the Roche monitors, project Statisticians or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would impact subject treatment. The Investigator should make every effort to contact Roche before unblinding a patient's treatment assignment, but must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study subjects for another purpose must be discussed with Roche.

When required, unblinding will be performed by means of an Interactive Voice Response System (IVRS) or an equivalent method.

As per regulatory reporting requirement, Roche will unblind the identity of the study medication for all unexpected serious adverse events that are considered by the Investigator to be related to study drug. Details of subjects who are unblinded during the study will be included in the Clinical Study Report (CSR).

The password-protected and/or encrypted electronic Master Randomization or Master Medication List is kept by Clinical Supply in their secure system and is only accessible to the Randomization List Managers. No open key to the code will be available at the study center, to the Roche monitors, project statisticians, or to the project team at Roche.

Unblinding for MRI-C, iDMC, and PK/PD analysis groups (which are independent from the project team) will be performed according to Roche standard procedures.

During the open label Part 3, gantenerumab treatment will be allocated by IxRS based on the titration schedule assigned for the APOE ε4 carriers (i.e., 1ε4 and 2ε4) and non-carriers (0ε4).

6.5 Accountability of IMP and Assessment of Compliance

6.5.1 Accountability of IMP

The Investigator is responsible for the control of drugs under investigation. Adequate records for the receipt (e.g., Drug Receipt Record) and disposition (e.g., Drug Dispensing Log) of the study drug must be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records.

Accurate records must be kept for each study drug provided by the sponsor. These records must contain the following:

- Documentation of drug shipments received from the Sponsor (date received and quantity)
- Disposition of unused study drug not dispensed to subject

A Drug Dispensing Log must be kept current and should contain the following information:

- The identification of the subject to whom the study medication was dispensed
- The date[s], quantity of the study medication dispensed *to* the subject

All records and drug supplies must be available for inspection by the Monitor at every monitoring visit.

When the study is completed, the Investigator will return all empty, partially used, and unused containers of study drug to Roche unless site has received alternate authorization from Roche. The completed Drug Dispensing Log and Drug Return Record(s) will be returned to Roche unless alternate destruction has been authorized by Roche or required by local or institutional regulations (Section *6.5.2*). The Investigator's copy of the Drug Return Record(s) must accurately document the return of all study drug supplies to Roche.

6.5.2 Assessment of Compliance

Subject compliance will be assessed by maintaining adequate study drug dispensing records. The Investigator is responsible for ensuring that dosing is administered in compliance with the protocol. Delegation of this task must be clearly documented and approved by the Investigator.

6.6 Destruction of the IMP/Comparator

Local or institutional regulations may require immediate destruction of used investigational medicinal product (IMP) for safety reasons. In these cases, it may be acceptable for investigational site staff to destroy dispensed IMP before a monitoring inspection provided that source document verification is performed on the remaining inventory and reconciled against the documentation of quantity shipped, dispensed, returned and destroyed. Written authorization must be obtained from the Sponsor at study start up before destruction.

If there are any issues with the drug it should be returned to the appropriate Roche clinical trial supplies department for long-term storage and not destroyed.

Written documentation of destruction must contain the following:

- Identity (batch numbers or participant identification numbers) of IMP and comparator destroyed
- Quantity of IMP destroyed
- Date of destruction
- Method of destruction
- Name and signature of responsible person who destroyed investigational products.

7. SAFETY INSTRUCTIONS AND GUIDANCE

7.1 Adverse Events (AEs)

7.1.1 Clinical Adverse Events

According to the International Conference of Harmonization (ICH), an AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product*, regardless of causal attribution*. An AE can therefore be any *of the following:*

- *Any* unfavorable and unintended sign [including an abnormal laboratory finding], symptom, or disease temporally associated with the use of a medicinal [investigational] product, whether or not considered related to the medicinal [investigational] product.
- *Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition)*
- *Recurrence of an intermittent medical condition (e.g., headache) not present at baseline*
- *Any deterioration in a laboratory value or other clinical test (e.g., ECG, X-ray) that is associated with symptoms or leads to a change in study treatment or concomitant treatment or discontinuation from study drug*
- *Adverse events that are related to a protocol-mandated intervention, including those that occur prior to assignment of study treatment (e.g., screening invasive procedures such as biopsies)*

A consistent methodology of non-directive questioning should be adopted for eliciting adverse event information at all patient evaluation timepoints. Examples of non-directive questions include the following:

> *"How have you felt since your last clinic visit?"*
>
> *"Have you had any new or changed health problems since you were last here?"*

7.1.1.1 Intensity

All clinical AEs encountered during the clinical study will be reported on the AE eCRF. Intensity of AEs will be graded on a three-point scale [mild, moderate, severe] and reported in detail on the AE eCRF.

Mild	*Discomfort noticed, but no disruption of normal daily activity.*
Moderate	*Discomfort sufficient to reduce or affect normal daily activity.*
Severe	*Incapacitating with inability to work or to perform normal daily activity.*
Note: Regardless of severity, some events may also meet seriousness criteria. Refer to definition of a serious adverse event (see Section 7.1.1.3).	

7.1.1.2 Drug–Adverse Event Relationship (Assessment of Causality of Adverse Events)

Relationship of the AE to the treatment should always be assessed by the investigator. *Investigators or their designees should use their knowledge of the patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an adverse event is considered related to the study drug, indicating "yes" or "no" accordingly.*

To ensure consistency of causality assessments, investigators should apply the following general guidelines:

- *Temporal relationship of event onset to the initiation of study drug*
- *Course of the event, considering especially the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (where applicable)*
- *Known association of the event with the study drug or with similar treatments*
- *Known association of the event with the disease under study*
- *Presence of risk factors in the patient or use of concomitant medications known to increase the occurrence of the event*
- *Presence of non-treatment-related factors that are known to be associated with the occurrence of the event*

Causal Attribution Guidance

Is the AE/SAE suspected to be caused by the investigational product based on facts, evidence, science-based rationales, and clinical judgment?	
Yes	*There is a plausible temporal relationship between the onset of the adverse event and administration of the study drug, and the adverse event cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies; and/or the adverse event follows a known pattern of response to the study drug; and/or the adverse event abates or resolves upon discontinuation of the study drug or dose reduction and, if applicable, reappears upon re challenge.*
No	*An adverse event will be considered related, unless it fulfills the criteria specified below.* *Evidence exists that the adverse event has an etiology other than the study drug (e.g., preexisting medical condition, underlying disease, intercurrent illness, or concomitant medication); and/or the adverse event has no plausible temporal relationship to administration of the study drug (e.g., cancer diagnosed 2 days after first dose of study drug).*

7.1.1.3 Serious Adverse Events [Immediately Reportable to Sponsor]

A Serious Adverse Event is any AE that at any dose fulfils at least one of the following criteria:

- is fatal; [results in death; NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity *(i.e., the adverse event results in substantial disruption of the patient's ability to conduct normal life functions)*
- is a congenital anomaly/birth defect *born to a mother exposed to study drug*
- is medically significant *in the investigator's judgment (e.g., may jeopardize the patient or may* require intervention to prevent one or other of the outcomes listed above*)*

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (e.g., rated as mild, moderate, or severe, see Section 7.1.1.1); the event itself may be of relatively minor medical significance (such as severe headache without any further findings). Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

The study will comply with all local regulatory requirements and adhere to the full requirements of the ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2.

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in this section), except as outlined below.

An event that leads to hospitalization under the following circumstances should not be reported as an adverse event or a serious adverse event:

- Hospitalization for respite care
- Hospitalization for a pre-existing condition, provided that the following criterion is met:
  - The hospitalization was planned prior to the study or was scheduled during the study when elective surgery became necessary because of the expected normal progression of a disease present at baseline
- The study subject has not suffered an adverse event

In centers where it is standard practice to hospitalize a subject for an LP for observation, this hospitalization itself would not be considered a serious adverse event. If the hospitalization is extended due to an adverse event, this would be considered an SAE.

7.1.1.4 Adverse Events of Special Interest (Immediately Reportable to the Sponsor)

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.2.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- *Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 7.1.2)*
- *Suspected transmission of an infectious agent by the study drug, as defined below*

  Any organism, virus, or infectious particle (e.g., prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of the study drug is suspected.

7.1.2 Laboratory Test Abnormalities

Laboratory test results will appear on electronically produced laboratory reports submitted directly from the central laboratory.

Any laboratory result abnormality fulfilling the criteria for a serious adverse event should be reported as such on the AE eCRF. Any treatment-emergent abnormal laboratory result which is clinically significant, i.e., meeting one or more of the following conditions, should be recorded as a single event on the AE eCRF:

- Accompanied by clinical symptoms
- Leading to a change in study medication [e.g., dose modification, interruption or permanent discontinuation]
- Requiring a change in concomitant therapy [e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment].
- *Results in a medical intervention (e.g., potassium supplementation for hypokalemia)*
- *Is clinically significant in the investigator's judgment*

This applies to any protocol and non-protocol specified safety and efficacy laboratory result from tests performed after signing of the informed consent, which falls outside the laboratory reference range and meets the clinical significance criteria.

It is the investigator's responsibility to review all laboratory findings. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an adverse event.

If a clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 × ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

If a clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded on the Adverse Event eCRF, along with a descriptor indicating whether the test result is above or below the normal range (e.g., "elevated potassium," as opposed to "abnormal potassium"). If the laboratory abnormality can be characterized by a precise clinical term per standard definitions, the clinical term should be recorded as the adverse event. For example, an elevated serum potassium level of 7.0 mEq/L should be recorded as "hyperkalemia."

The finding of an elevated ALT or AST (>3×ULN) in combination with either an elevated total bilirubin (>2×ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury *(as defined by Hy's Law)*. Therefore, Investigators must report as an adverse event *of special interest (Section 7.1.1.4) if* the occurrence of either of the following:

- Treatment-emergent ALT or AST >3 × ULN in combination with total bilirubin >2 × ULN
- Treatment-emergent ALT or AST >3 × ULN in combination with clinical jaundice.

If a patient develops moderate to severe neutropenia (ANC <1000/mm3) in the absence of an identified cause, investigators should consider temporary discontinuation of the study drug. Neutrophil counts should be monitored according to the local guidelines. Reintroduction of study drug could be done only after the investigator discusses the case with the Sponsor's Medical Monitor.

7.1.2.1 Follow-up of Abnormal Laboratory Test Values

In the event of medically significant unexplained abnormal laboratory test values, the tests should be repeated and followed up until they have returned to the normal range and/or an adequate explanation of the abnormality is found.

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

7.1.3 Abnormal Vital Sign Values

Not every vital sign abnormality qualifies as an adverse event. A vital sign result must be reported as an adverse event if it meets any of the following criteria:

- *Is accompanied by clinical symptoms*
- *Results in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)*
- *Results in a medical intervention or a change in concomitant therapy*
- *Is clinically significant in the investigator's judgment*

It is the investigator's responsibility to review all vital sign findings. Medical and scientific judgment should be exercised in deciding whether an isolated vital sign abnormality should be classified as an adverse event.

If a clinically significant vital sign abnormality is a sign of a disease or syndrome (e.g., high blood pressure), only the diagnosis (i.e., hypertension) should be recorded on the Adverse Event eCRF.

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF.

7.1.4 MRI Observations

Any treatment-emergent MRI observations, ARIA-E, and ARIA-H, as well as other clinically relevant findings that *are clinically significant (i.e., meeting one or more of the following conditions) should be recorded as a single event on the AE eCRF:*

- *Accompanied by clinical symptoms*

- *Leading to a change in study medication (e.g., dose modification, interruption or permanent discontinuation)*
- *Requiring a change in concomitant therapy (e.g., addition of, interruption of, discontinuation of, or any other change in a concomitant medication, therapy or treatment)*
- *Results in a medical intervention*
- *Is clinically significant in the investigator's judgment*

All such MRI observations will also be compiled in a separate MRI report. In addition, adverse events considered to be symptoms of ARIA will be marked as such in the eCRF. These events will be summarized separately in the CSR. To further elucidate potential clinical implications of ARIA findings, patients will be asked within 1 week before each MRI, by non-directive, unbiased questioning, if they experience CNS adverse events. The adverse events collected in this prospective fashion will be distinct from other adverse events and summarized separately in the clinical study report. Additional data on associated symptoms (as defined on the eCRF) and safety MRI scans will be collected for these adverse events.

7.1.5 Adverse Events Associated with an Overdose or Error in Drug Administration

An overdose is the accidental or intentional use of a drug in an amount higher than the dose being studied. An overdose or incorrect administration of any drug including study treatment is not itself an adverse event, but it may result in an adverse event. All adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF. If the associated adverse event fulfills serious criteria, the event should be reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 7.1.1.3).

Any study drug overdose or incorrect administration of study drug should be noted on the Study Drug Administration eCRF.

7.1.6 *Deaths*

All deaths that occur during the protocol-specified adverse event reporting period (see Section 7.1.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 7.2.2). This includes death attributed to progression of AD.

Death should be considered an outcome and not a distinct event. The event or condition that caused or contributed to the fatal outcome should be recorded as the single medical concept on the Adverse Event eCRF. Generally, only one such event should be reported. If the cause of death is unknown and cannot be ascertained at the time of reporting, ***"unexplained death"*** *should be recorded on the Adverse Event eCRF. If the cause of death later becomes available (e.g., after autopsy), "unexplained death" should be replaced by the established cause of*

death. The term ***"sudden death"*** *should not be used unless combined with the presumed cause of death (e.g., "sudden cardiac death").*

If the death is attributed to progression of AD, "Alzheimer's disease progression" should be recorded on the Adverse Event eCRF.

7.2 Handling of Safety Parameters

7.2.1 Reporting of Adverse Events

Collection of adverse events begins at the time the informed consent is signed and continues throughout the study, including the follow-up period. All AEs will be recorded in detail on the source documents and on the AE eCRF for subjects who are randomized to study treatment.

7.2.2 Reporting of Serious Adverse Events *and Adverse Events of Special Interest* [Immediately Reportable]

For reports of serious adverse events and adverse events of special interest, investigators should record all case details that can be gathered immediately (i.e., within 24 hours) on the Adverse Event eCRF and submit the report via the electronic data capture (EDC) system. A report will be generated and sent to Roche Safety Risk Management by the EDC system.

In the event that the EDC system is unavailable, a paper Serious Adverse Event Reporting Form and fax cover sheet should be completed and faxed to Roche Safety Risk Management or its designee immediately (i.e., no more than 24 hours after learning of the event). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

After informed consent *has been obtained*, but prior to initiation of study medication, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to MRIs or invasive procedures such as lumbar punctures). *After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until the last visit. After this period, the investigator should report any serious adverse events that are believed to be related to study drug treatment.*

Related Serious Adverse Events MUST be collected and reported regardless of the time elapsed from the last study drug administration, even if the study has been closed.

Unrelated Serious Adverse Events must be collected during the study *until the last study visit.*

If the study is closed but a SAE occurs within required reporting period, the SAE worksheet is used to report the event to the sponsor.

This study adheres to the definition and reporting requirements of ICH Guideline for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2. Complete information can be found in Appendix 1.

7.2.3 Reporting of Pregnancy

A female subject must be instructed to immediately inform the Investigator if she becomes pregnant during the study. She will then be discontinued from study medication. The Investigator should report all pregnancies within 24 hours to the Sponsor. The Investigator should counsel the subject; discuss the risks of continuing with the pregnancy and the possible effects on the fetus. Monitoring of the subject should continue until conclusion of the pregnancy. Pregnancies that occur up to 16 weeks after the last dose of study medication must also be reported to the Investigator.

The site must report the pregnancy on the Pregnancy Report eCRF for randomized subjects. If the study is closed but pregnancy occurs within required reporting period, the Pregnancy Report worksheet is used to report the event to the sponsor.

Any spontaneous abortion should be classified as a serious adverse event (because the Sponsor considers spontaneous abortions to be medically significant events), recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

Any congenital anomaly/birth defect in a child born to a female patient should be classified as a serious adverse event, recorded on the Adverse Event eCRF, and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event).

7.2.4 Reporting Requirements for Medical Device Complaints

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study patient, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event).

7.2.5 Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Ethics Committees

Any treatment-emergent SAE deemed related to gantenerumab will be reported as a suspected unexpected serious adverse reaction (SUSAR) and will be reported to investigators at each site and associated Institutional Review Boards (IRBs)/Ethics Committees (ECs).

The Sponsor will promptly evaluate all serious adverse events and adverse events of special interest against cumulative product experience to identify and

expeditiously communicate possible new safety findings to investigators, IRBs, ECs, and applicable health authorities based on applicable legislation.

To determine reporting requirements for single adverse event cases, the Sponsor will assess the expectedness of the events using the Gantenerumab IB.

The Sponsor will compare the severity of each event and the cumulative event frequency reported for the study with the severity and frequency reported in the Gantenerumab IB.

Reporting requirements will also be based on the investigator's assessment of causality and seriousness, with allowance for upgrading by the Sponsor as needed.

7.2.6 Recording Adverse Events on the eCRF

Investigators should use correct medical terminology/concepts when recording AEs or SAEs on the AE eCRF. Avoid colloquialisms and abbreviations.

Only one medical concept should be recorded in the event field on the AE eCRF.

In general, adverse events that are secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause, with the exception of severe or serious secondary events. A medically significant secondary adverse event that is separated in time from the initiating event should be recorded as an independent event on the Adverse Event eCRF. For example:

- *If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.*
- *If vomiting results in severe dehydration, both events should be reported separately on the eCRF.*
- *If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.*
- *If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.*
- *If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.*

All adverse events should be recorded separately on the Adverse Event eCRF if it is unclear as to whether the events are associated.

A persistent adverse event is one that extends continuously, without resolution, between patient evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF, unless the severity increases. If a persistent adverse event becomes more severe, it should be recorded as a separate event on the Adverse Event eCRF. The initial (less severe) adverse event report should be

updated to indicate that the event resolved on the date just prior to the day the event became more severe. If a persistent adverse event becomes serious, it should be recorded as a separate event on the Adverse Event eCRF and reported to the Sponsor immediately (i.e., no more than 24 hours after learning that the event became serious; see Section 7.2.2 for reporting instructions). The initial (non-serious) adverse event report should be updated to indicate that the event resolved on the date just prior to the day the event became serious.

A recurrent adverse event is one that resolves between patient evaluation timepoints and subsequently recurs. Each recurrence of an adverse event should be recorded separately on the Adverse Event eCRF.

Individual signs and symptoms of injection-site reactions (e.g., erythema, pruritus, pain) should be reported on the dedicated Injection Site Reaction eCRF. The overall diagnosis of injection site reaction should be captured on the Adverse Event eCRF. Systemic reactions should be recorded as a single diagnosis.

For adverse events other than injection-related reactions, a diagnosis (if known) should be recorded on the Adverse Event eCRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded on the Adverse Event eCRF. Ifa diagnosis is subsequently established, all previously reported adverse events based on signs and symptoms should be nullified and replaced by one adverse event report based on the single diagnosis, with a starting date that corresponds to the starting date of the first symptom of the eventual diagnosis

7.2.7 Follow-up of Patients after Adverse Events

7.2.7.1 Investigator Follow-Up

The investigator should follow each adverse event until the event has resolved to baseline grade or better, the event is assessed as stable by the investigator, the patient is lost to follow-up, or the patient withdraws consent. Every effort should be made to follow all serious adverse events considered to be related to study drug or trial-related procedures until a final outcome can be reported.

During the study period, resolution of adverse events (with dates) should be documented on the Adverse Event eCRF and in the patient's medical record to facilitate source data verification.

All pregnancies reported during the study should be followed until pregnancy outcome.

7.2.7.2 Sponsor Follow-Up

For serious adverse events, adverse events of special interest, and pregnancies, the Sponsor or a designee may follow up by telephone, fax, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

7.3 Safety Plan

To date, ARIA findings and injection site reactions are the identified risks of gantenerumab.

Detailed information about ARIA findings is provided in Section 1.3.3. [redacted] *In case of clinical symptoms, the use of IV glucorticosteroids may be considered.*

Concerning injection site reactions, gantenerumab is generally well tolerated by patients. Injection-site reactions have been observed in up to one-third of healthy volunteers after SC administration (Section 1.1.2.2). As of 13 February 2018, injection site reactions have been reported in 25.3% and 29.8% of patients treated with gantenerumab in the OLE periods of Study WN25203 and Study WN28745, respectively. All injection site reactions were non-serious, with the majority being mild and resolving without treatment. Approximately 10% of patients who had injection site reactions required treatment, which included topical steroids and antihistamines.

No gantenerumab-related immunogenicity reactions of major clinical relevance have emerged to date. Patients should be monitored for and alerted to the risk of any symptoms of hypersensitivity reactions.

Refer to the Gantenerumab IB for information about identified and potential risks.

8. STATISTICAL CONSIDERATIONS AND ANALYTICAL PLAN

The plans for the statistical analysis of the data recorded during Part 1, the first 24 months of double-blind treatment are summarized below. The plans for the analysis of the data recorded during Part 2, the extension are described in section 8.6. The plans for the analysis of the data recorded during Part 3, the open-label extension are described in Section 8.7.

8.1 Primary and Secondary Study Endpoints

8.1.1 Primary Efficacy Endpoint

Change from baseline in CDR-SOB score at Week 104.

8.1.2 Secondary Efficacy Endpoints

8.1.2.1 Cognition – Change from Baseline at Week 104 in the Following

- Alzheimer's Disease Assessment Scale – Cognition (ADAS-Cog) total score
- Mini Mental State Exam (MMSE) total score
- CANTAB – selected subtest scores
  - Simple Reaction Time (RTI)
  - Simple Movement Time (RTI)
  - 5- Choice Reaction Time (RTI)
  - Delayed Match to Sample (DMS)
  - Spatial Working Memory (SWM)
  - Pattern Recognition Memory (PRM) immediate
  - Pattern Recognition Memory (PRM) delayed
  - Rapid Visual Information Processing (RVP)
  - Paired Associates Leaning (PAL)
- FCSRT-IR

8.1.2.2 Global

- CDR global score at Week 104

8.1.2.3 Functioning

- FAQ total score change from baseline at Week 104

8.1.2.4 Neuropsychiatric Functioning

- Neuropsychiatric Inventory (NPI-Q) –total and domain scores change from baseline at Week 104

8.1.2.5 Dementia Assessment

- Time from baseline to development of dementia

8.1.2.6 MRI Volumetric Measures

- Hippocampal volume change from baseline
- Whole brain volume change from baseline
- Ventricular enlargement change from baseline
- Change from baseline in other volumetric measures such as cortical thickness

8.1.2.7 Cerebrospinal Fluid Biomarker Measures

- Change from baseline in CSF T-tau, P-tau, and Aβ1-42 levels

8.1.3 Safety

- MRI safety findings: inflammation (such as that found on FLAIR sequences), microbleeds and other.
- Adverse events
- Physical and neurological examination
- GDS
- C-SSRS
- Vital signs
- ECG
- Clinical laboratory results

8.1.4 Pharmacokinetics

- C_{max}
- Time to peak concentration (T_{max})
- Trough plasma concentration at steady state (C_{min})
- Area under the time-plasma concentration curve at steady state ($AUC_{0-\tau}$)

Other parameters determined from the pharmacokinetic model will be regarded as secondary. Potential covariates for the model will be explored as appropriate.

8.1.5 Exploratory Endpoints

8.1.5.1 Plasma Biomarkers

- Plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ change from baseline

8.1.5.2 Genotype

The following information will be used to assess its impact on efficacy and safety:

- ApoE genotype
- FcγR genotype

8.2 Statistical and Analytical Methods

All efficacy data in Part 1, up to week 104 will be evaluated in the following manner:

- Each of the two gantenerumab dose groups (i.e., 105 mg or 225 mg) versus placebo. The gantenerumab 225 mg group will include only subjects with the ApoE 0ε4 and 1ε4 types; therefore, for the primary comparison of the gantenerumab 225 mg group to placebo, the comparator group will include the subset of placebo subjects who have the ApoE 0ε4 and 1ε4 types. For the primary comparison of the gantenerumab 105 mg group to placebo, the comparator group will be the entire set of subjects randomized to placebo. The primary inferential statistics will be applied to the pairwise comparisons of each of the 2 gantenerumab dose groups to the corresponding placebo group.
- All gantenerumab dose groups combined (i.e., 105 mg plus 225 mg) versus placebo for overall assessments regardless of the ApoE genotype. All placebo subjects will be pooled.

All analyses in Part 2 will be considered exploratory.

8.2.1 Efficacy Data

8.2.1.1 Primary Efficacy Variable

For the assessment of differences between each gantenerumab group and placebo with regard to the mean change from baseline in the CDR SOB score at week 104, a mixed-effects MMRM analysis incorporating data up to 104 weeks of treatment will be used to utilize all the data collected over time with consideration of the variance-covariance matrix of the repeated measures. This method allows a general unstructured variance-covariance matrix and enables to include data from subjects with incomplete data across scheduled time points.

The following null (H_0) and alternative (H_a) hypotheses will be tested to compare the mean change values between each of the gantenerumab groups and placebo group:

$$H_0: MEAN_{RO} = MEAN_{placebo} \text{ versus}$$

$$H_a: MEAN_{RO} \neq MEAN_{placebo}$$

where $MEAN_{RO}$ and $MEAN_{placebo}$ refer to mean change of gantenerumab and placebo, respectively.

The model will include the change from baseline in the CDR–SOB score as the dependent variable. The effects in the model will include independent variables of the fixed, categorical effects of treatment, assessment weeks relative to the first dose of study medication (i.e., time), and treatment-by-time interaction, and ApoE status (carrier vs. non-carrier), along with covariates of the baseline value and hippocampal volume at baseline. Time will be treated as the repeated variable within a subject. Subject, treatment, and time will be treated as class variables. An unstructured variance-covariance structure will be applied to model the within-subject errors.

As a sensitivity analysis for the primary efficacy variable, the MMRM model excluding the hippocampal volume at baseline covariate will also be run**.** Sensitivity analyses will also be performed excluding the ApoE4 genotype carrier status as an additional fixed effect in the statistical model in order to assess the impact of this factor on the primary and selected secondary efficacy variables.

Sensitivity analyses to assess the impact of missing data on the primary efficacy endpoint results will be performed using multiple imputation and pattern-mixture method models. Additional details will be provided in the Statistical Analysis Plan.

A treatment-by-time interaction contrast will be constructed to estimate the difference between each of the gantenerumab doses and placebo in mean change from baseline to week 104. Based on the analysis above, least square means, standard errors, and the 95% confidence intervals of treatment difference will be reported for each dose of gantenerumab against placebo.

In order to adjust for the multiplicity in the pairwise comparisons of each gantenerumab dose to placebo, a hierarchical testing procedure will be used.

8.2.1.2 Secondary Efficacy Variables

Continuous Variables

The secondary efficacy variables of the continuous type with multiple post-baseline scheduled assessments will be analyzed using the same methods described above for the primary efficacy variable: MMRM including the covariate of hippocampal volume at baseline.

Time-to-Event Variable

The time-to-onset of dementia from baseline will be analyzed using an un-stratified log rank test. The following hypothesis will be tested:

H_0: There is no difference in the survival functions between the gantenerumab (RO) and placebo (pbo) group:

$$SUR_{RO} = SUR_{pbo}, \quad \text{where SUR denoted the distribution function.}$$

H_a: there is a difference in the survival function between the gantenerumab (RO) and placebo (pbo) group:

$$SUR_{RO} \neq SUR_{PBO}, \quad \text{where SUR denoted the distribution function.}$$

In addition, a stratified log rank test of treatment difference will be performed as an exploratory analysis of this variable, using ApoE genotype status (carrier vs. non-carrier) as a stratification factor. If the number of events observed in any treatment-by-genotype status cell is less than 2, then this exploratory analysis will not be performed. Additional exploratory analyses will be performed as appropriate using clinically relevant covariates such as baseline biomarker variables. For this variable, the principal analysis results will be those generated using the unstratified log-rank test.

When comparing time-to-event endpoints between treatment groups, it is important to assess whether there are systematic differences in the completeness and duration of follow-up. Summaries of follow-up duration by treatment group will be provided for all subjects and for subjects who have not had an event yet. The duration of follow-up will be calculated as the interval (days) from the first day of study treatment to the event or date last known to have not the event.

8.2.2 Safety Data

All safety variables will be summarized for each assessment time (including follow-up) using descriptive statistics. Incidence of adverse events will be summarized by treatment group based on body systems and dictionary preferred terms. Incidence of marked abnormal lab test results will be summarized. All the GDS ratings, anti-drug antibody, lab tests, ECG, and vital signs will be summarized (e.g., mean, median, SD or frequency of abnormalities) for each assessment time by treatment group. ECG data will also be analyzed to evaluate treatment effect on QT parameters as described in the FDA guidance document.

All the safety data collected during the follow-up period (i.e., after discontinuation of study treatment) will be summarized separately from the data collected during the treatment period.

Number (%) of subjects with MRI safety findings will be summarized at each scheduled visit by treatment and MRI safety finding types. In addition, number (%) of subjects with MRI findings will be summarized by ApoE genotypes and MRI safety finding types.

8.2.3 Exploratory Analysis

The following 2 types of analyses will be performed to explore association of the treatment effect with the subject's genotypes and biomarkers:

- To assess influence of the ApoE and FCγR genotypes on the gantenerumab treatment effect, the primary efficacy variable and selected safety parameters will be summarized by each of the genotypes. Inferential statistics may be applied in case the difference is clinically relevant.
- To evaluate effect of gantenerumab treatment on changes in plasma $A\beta_{1-40}$ and $A\beta_{1-42}$ biomarkers; changes will be summarized for each treatment group, i.e., each dose of gantenerumab and placebo.

8.2.4 Subgroup Analyses

The results of selected efficacy and safety variables will be summarized within subgroups using descriptive statistics. Additional exploratory analyses of efficacy results may be performed using an MMRM model, with the subgroup, a treatment-by-subgroup interaction, and a subgroup-by-time interaction terms included along the independent effects described above. Such exploratory analyses will be performed primarily in the case where the descriptive statistics results indicate substantial differences between the subgroups.

The following variables will be used to define the subgroups for these analyses:

- Sex
- Age
- Race
- ApoE status
- FcγR genotype
- Region

8.3 Sample Size

The comparison of the gantenerumab 225 mg arm to the placebo arm will include primary efficacy results from the approximately 257 subjects randomized to gantenerumab 225 mg, and the approximately 213 ApoE 0ε4 and 1ε4 subjects randomized to placebo. A total of 770 subjects will warrant at least 80% power in demonstrating an effect size of 0.35 (gantenerumab 225 mg vs. placebo) at the type I error level of $p \leq 0.05$ (2-sided). In order to protect the overall type I error at the 0.05 level, a hierarchical testing procedure will be used in which the first hypothesis to be tested will be the comparison of the gantenerumab 225 mg group to the corresponding placebo group. The second test, comparing the gantenerumab 105 mg group to the placebo group, will be carried out only if the first test is statistically significant at the 2-sided 0.05 level.

The power calculation was based on simulations of the MMRM analysis planned for analysis of the primary efficacy variable. The following assumptions were included:

- 4 post-baseline assessment visits at Weeks 24, 52, 76, and 104.
- Overall dropout rate of 30% at Week 104 for both placebo and active treatment group, incremental rates over the 104 week period.
- Effect sizes of 0.35 (gantenerumab 225 mg vs. placebo) and 0.25 (gantenerumab 105 mg vs. placebo) at Week 104 assuming increasing magnitude of treatment difference over the 104 weeks period.
- A correlation structure with stronger correlations for assessments that are adjacent in time and weaker between assessments that are further apart.
- About 5% reduction in sample size with hippocampal volume at baseline as a covariate in the analysis.

The sample size was confirmed following a planned blinded evaluation of the variance in the change in the CDR-SOB at Week 76 (Section 10.2.2).

8.3.1 Analysis Populations

8.3.1.1 Safety Population

The safety population will consist of all subjects who have received any dose of study medication, whether withdrawn prematurely or not. All safety data will be analyzed according to the medication actually taken.

8.3.1.2 Intent-to-Treat Population

The intent-to-treat (ITT) population will include all subjects who received any dose of study treatment and had at least 1 post-baseline assessment of CDR SOB. The ITT analysis will be done by randomized treatment.

The ITT population will be the primary population for all analyses of primary and secondary efficacy variables as well as the imaging and biomarker and clinical efficacy variables.

8.3.1.3 Per-Protocol Population

The per-protocol (PP) population may be defined as a subset of the intent-to-treat population. Definition of the PP population will be finalized before the clinical database closure and will be documented in the analysis plan. The definition will include those who did not have any major protocol violations that affect efficacy evaluation. For the PP population analysis, data will be analyzed according to the treatment actually taken. The primary efficacy variables will be analyzed including the PP population when there is a more than 10% difference in number of subjects between ITT and PP population.

8.4 Interim Analysis

Two interim analyses will be performed, as described in Section 10.2.

8.5 Other Analyses

8.5.1 Pharmacokinetic Analysis

Nonlinear mixed effects modeling will be used to analyze the dose-concentration-time data of gantenerumab. Information from other studies in humans may be incorporated to

establish the pharmacokinetic model. The selection of parameters and the derivation of individual measures of exposure, such as $AUC_{0-\tau}$, C_{max}, and trough concentrations (C_{trough}) will depend on the final pharmacokinetic model used for this analysis. All pharmacokinetic parameters will be presented by listings and descriptive summary statistics including arithmetic mean (for $AUC_{0-\tau}$, C_{max}, and C_{trough}), median, range, standard deviation, and CV. Results of this analysis will be reported separately.

If appropriate, concentration-effect relationships may be explored and modeled post hoc for pharmacodynamic, efficacy or safety measures.

8.6 Analysis Considerations for Data Collected during Part 2, the Extension Period for Continued Double-Blind Treatment

All data collected during Part 2 the extension will be summarized using descriptive statistics as described above. No formal hypothesis testing or inferential statistics will be performed for the data collected during this extension period.

All subjects included in the safety and ITT populations (as defined in Sections 8.3.1.1 and 8.3.1.2) who choose to continue double-blind treatment after dose 26 will be included in the respective analysis populations for the analysis of the extension period data.

For all analyses of efficacy data collected during Part 2, the extension period, a sensitivity analysis will be performed in which subjects who start symptomatic treatments for Alzheimer's disease will be censored for purposes of analysis at the time at which the treatment is initiated. Any efficacy assessments made after the start of such symptomatic treatments will be flagged as such in data listings.

8.7 Analysis Considerations for Data Collected during Part 3 – the Open-Label Extension

Statistical analyses will primarily focus on safety aspects during and after the up-titration phase in Part 3 of the trial. In addition, it is planned that efficacy analyses will be conducted on cognitive and functional measures as well as biomarkers. It is planned that efficacies will be calculated using both, the original, drug-naïve baseline as well as the baseline that gets available before start of *Part* 3. Results of these analyses will be interpreted in an exploratory fashion. The number of subjects *enrolled in Part 3 is 154*.

9. DATA COLLECTION, MANAGEMENT AND QUALITY ASSURANCE

The overall procedures for quality assurance of clinical study data are described in the Roche Standard Operational Procedures.

Electronic Case Report Forms are to be completed by the site using the Medidata Rave Electronic Data Capture (EDC) system. Sites will transcribe data from source documents onto the eCRFs. In no case is the eCRF to be considered as source data for this trial. Sites will receive training and help text for appropriate eCRF completion. eCRFs will be electronically transmitted to Roche and should be handled in accordance with instructions from Roche.

In the event of discrepant data, Roche will electronically request data clarification from the sites, which the sites will resolve electronically, in the EDC system. Roche will produce an EDC Study Logic and Check Specification document that describes the data quality checking to be performed on the data in Rave.

Accurate and reliable data collection will be assured by verification and cross–check of the eCRFs against the Investigator's source documents by the study monitor (source document verification), and the maintenance of a drug–dispensing log by the Investigator.

A comprehensive validation check program utilizing front-end checks in the eCRF and back-end checks in the Roche data base will verify the data and discrepancies will be generated accordingly. These are transferred electronically to the eCRF at the site for resolution by the Investigator.

Throughout the study the study management team (SMT) will review data according to the SMT Integrated Data Review Plan.

9.1 Assignment of Preferred Terms and Original Terminology

For classification purposes, preferred terms will be assigned by the Sponsor to the original terms entered on the eCRF, using the most up-to-date version of the Medical Dictionary for Regulatory Activities (MedDRA) terminology for adverse events and diseases and the Genentech Drug Dictionary for treatments and surgical and medical procedures.

10. REVIEW OF RESULTS DURING THE CONDUCT OF THE STUDY

10.1 Review of Safety Data

The study will have 2 committees for the purpose of reviewing and recommending actions to be taken on the basis of safety data. There will be an independent MRI-C as well as a separate iDMC. Each committee is described briefly below and each will have a separate charter providing specifics on the operations of the committee, including how the treatment disclosures will be managed.

10.1.1 MRI Review Committee

The MRI-C will review any relevant new MRI findings identified by the MRI central reader and will provide guidance on the management of subjects, taking into account the guidelines in the protocol. The committee may request that measures in addition to those in the protocol be undertaken (e.g., a repeat MRI earlier than 4 weeks). The committee can also make recommendations to alter the protocol procedures for the management of subjects with MRI abnormalities as well as recommendations for amendments to the protocol. During Parts 1 and 2, the committee reviewed MRI findings as described in Section 5.1.3 and 5.1.4.3, respectively. In Part 3, the committee will review relevant MRI findings as defined in the MRI-C Charter.

10.1.2 Independent Data Monitoring Committee

An external fully iDMC, composed of three physicians and one statistician, met periodically as specified in the Charter to review the safety and key efficacy results from

the double-blind treatment phase. This committee was also provided with all new significant safety data events as they occurred, including relevant new MRI findings, and could have ad hoc meetings as necessary. This committee could request the study to be amended or terminated based on their findings (see also Section 10.2.3 Futility Analysis).

During the Part 3, the iDMC reviewed safety findings until the majority of subjects had reached the target dose. Significant MRI findings during Part 3 will continue to be reviewed by the IMC and by the MRI-C as documented in the MRI-C charter. Any new relevant findings identified either through the IMC or MRI-C may be submitted to the Phase III studies (WN29922 and WN39658) iDMC.

10.2 Interim Analysis

Two interim analyses, and one blinded sample size assessment, *were* planned. The specifics of each analysis *were* documented prior to its conduct in the Statistical Analysis Plan.

10.2.1 Administrative Interim Analysis

The administrative interim analysis was conducted approximately when the Week 52 visit for the 200th subject randomized was scheduled to occur. The main purpose of this review was to assess whether preparations for an additional adequate and well-controlled study should begin.

The review included unblinded PET scan results, safety (including safety MRI), ADA, biomarkers and pharmacokinetics. No efficacy data were included in this administrative interim analysis.

The type I error rate was not to be adjusted for this interim analysis as it is administrative (i.e., to gate the next steps of the development program).

The results will not be communicated to any of the study team members. The interim analysis results will be evaluated by the independent data monitoring committee and by a Roche review board that includes only senior Roche managers/scientists who are entirely separate from the study team. The Roche review board will not communicate any of the interim analysis results to any Roche personnel involved in the conduct of Study WN25203.

10.2.2 Sample Size Adjustment

At the time of the administrative interim analysis, a blinded evaluation of the observed variability in the absolute change from baseline in CDR-SOB at Week 76 was also performed. The analysis time point of Week 76 was selected for this analysis, as the number of subjects with available data at Week 104 would be insufficient to perform a meaningful analysis at this time.

Based on the data available at the time of the interim analysis, a point estimate and 1-sided 80% confidence bound for the standard deviation of the absolute change from baseline in CDR-SOB at Week 76 was calculated with the following assumption: if these results indicate a value substantially higher than the assumed value for this standard

deviation that was used in the process of determining the sample size (for example, if the lower bound of the confidence interval exceeds the assumed standard deviation value of 1.44), then the Sponsor will consider increasing the sample size of the study in order to maintain the desired power. The increase in sample size resulting from this analysis would be no more than 190 subjects (i.e., an increase from 770 to no more than 960 subjects), with the magnitude of the sample size increase depending on the number of subjects needed to maintain at least 80% power for the hypothesis testing of the primary endpoint. Based on the results of this analysis, the sample size remained as originally calculated (770 subjects).

10.2.3 Futility Analysis

A futility interim analysis was performed approximately when 50% of the sample size was scheduled to complete the Week 104 visit. This analysis was performed by the independent data coordinating center (iDCC) that generates the unblinded results reviewed by the iDMC on a regular basis, as described in Section 10.1.2. The iDMC reviewed the unblinded results for the primary efficacy endpoint (absolute change from baseline in CDR-SOB at Week 104). The analysis of the primary endpoint results at the time of this interim analysis indicated that the predictive probability of success for the trial is less than a pre-specified threshold, and the committee recommended that the trial could be terminated for futility. The iDMC communicated to the Roche Data Review Board only this recommendation (whether or not to either stop the study for futility); detailed results of the primary efficacy analysis were not shared with the Sponsor. The Roche Data Review Board has accepted this recommendation, and the dosing was suspended on 19 December 2014.

No adjustment for multiple comparisons was to be made to the α-level for this analysis, as the decision rules for the futility analysis will not allow for the opportunity to stop the study early for overwhelming efficacy.

The specifics of the analysis were documented prior to its conduct in an Interim Data Analysis Plan.

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PART II: ETHICS AND GENERAL STUDY ADMINISTRATION

12. ETHICAL ASPECTS

12.1 Local Regulations/Declaration of Helsinki

The Investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" or with the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study must fully adhere to the principles outlined in "Guideline for Good Clinical Practice" ICH Tripartite Guideline or with local law if it affords greater protection to the subject. For studies conducted in the EU/EEA countries, the Investigator will ensure compliance with the EU Clinical Trial Directive [2001/20/EC]. For studies conducted in the USA or under US IND, the Investigator will additionally ensure adherence to the basic principles of "Good Clinical Practice" as outlined in the current version of 21 Code of Federal Regulations, subchapter D, part 312, "Responsibilities of Sponsors and Investigators", part 50, "Protection of Human Subjects", and part 56, "Institutional Review Boards".

In other countries where a "Guideline for Good Clinical Practice" exists, Roche and the Investigators will strictly ensure adherence to the stated provisions.

12.2 Informed Consent

12.2.1 Main Study Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator [if acceptable by local regulations], to obtain signed informed consent from each subject prior to participating in this study after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study.

The Investigator or designee must also explain that the subjects are completely free to refuse to enter the study or to withdraw from it at any time, for any reason.

The clinical database for this study includes an eCRF for documenting subject informed consent, and this must be completed appropriately. If new safety information results in significant changes in the risk/benefit assessment, the consent form should be reviewed and updated if necessary. All subjects (including those already being treated) should be informed of the new information, given a copy of the revised form and give their consent to continue in the study.

12.2.2 Written Informed Consent from the Study Partner

It is a requirement for this study that the subject has a study partner considered reliable by the Investigator to provide accurate information as to the subject's cognitive and functional abilities and who agrees to accompany the subject to clinic visits which require their input for scale completion. Therefore separate study partner consent will be requested.

12.2.3 RCR Informed Consent

It is the responsibility of the Investigator, or a person designated by the Investigator (if acceptable under local regulations), to obtain written informed consent from each

individual who has consented to RCR sampling after adequate explanation of the aims, methods, objectives and potential hazards. Subjects must receive an explanation that they are completely free to refuse to provide the RCR specimen(s) and may withdraw his/her sample at any time and for any reason during the 15 year storage period of the specimen(s). The Informed Consent for an optional specimen donation will be incorporated as a specific section into the main Clinical Trial ICF. A second, separate, specific signature consenting to specimen donation will be required to document the study participant's agreement to provide an optional specimen; if the participant declines, he/she will check a "no" box in the appropriate section and not provide a second signature.

The clinical database for this study includes an eCRF for documenting subject informed consent to the RCR, and this must be completed appropriately.

12.2.4 Death or Loss of Competence of Participant who Has Donated a Specimen(s) That Is Stored in the RCR

In case of death or loss of competence, specimen and data will continue to be used as part of RCR research.

12.3 Independent Ethics Committee(IEC)/Institutional Review Board(IRB)

The protocol, informed consent and any accompanying material provided to the subject in the U.S. will be submitted by the Investigator to an IRB for review. For EEA member states, the Sponsor will submit to the Competent Authority and IEC, the protocol and any accompanying material provided to the subject. In both the U.S. and EEA member states, the accompanying material may include subject information sheets, descriptions of the study used to obtain Informed Consent and terms of any compensation given to the subject as well as advertisements for the trial.

An approval letter or certificate (specifying the protocol number and title) from the IEC/IRB must be obtained before study initiation by the Investigator specifying the date on which the committee met and granted the approval. This applies whenever subsequent amendments/modifications are made to the protocol.

Any modifications made to the protocol, Informed Consent or material provided to the subject after receipt of the IEC/IRB approval must also be submitted by the Investigator in the U.S. and by the Sponsor in the EEA member states in accordance with local procedures and regulatory requirements.

When no local review board exists, the investigator is expected to submit the protocol to a regional committee. If no regional committee exists, Roche will assist the Investigator in submitting the protocol to the European Ethics Review Committee.

Roche shall also submit an Annual Safety Report once a year to the IEC and CAs according to local regulatory requirements and timelines of each country participating in the study. In the U.S. Roche submits an IND Annual Report to the FDA according to local regulatory requirements and timelines.

Sampling for the RCR is contingent on review and approval for the exploratory biomarker assessments and written informed consent by an appropriate regulatory body (depending on the country where the study is performed) and a site's Institutional Review Board (IRB)/Ethics Committee (EC). If a regulatory or site's IRB/ EC does not approve the sampling for the exploratory assessments the section on biomarker sampling will not be applicable.

12.4 Role of the Science and Ethics Advisory Group (SEAG)

A Science and Ethics Advisory Group (SEAG), consisting of experts in the fields of biology, ethics, sociology, and law will advise Roche regarding the use of specimens stored in the RCR and on the scientific and ethical aspects of handling genetic information. The SEAG is independent of Roche.

13. CONDITIONS FOR MODIFYING THE PROTOCOL

Requests from Investigators to modify the protocol to ongoing studies will be considered only by consultation between an appropriate representative of the Sponsor and the Investigator [Investigator representative[s]. Protocol modifications must be prepared by a representative of the Sponsor and initially reviewed by all relevant functions and approved by the Disease Area Chair.

All protocol modifications must be submitted to the appropriate Independent Ethics Committee or Institutional Review Board for information and approval in accordance with local requirements, and to Regulatory Agencies if required. Approval must be obtained before any changes can be implemented, except for changes necessary to eliminate an immediate hazard to trial subjects.

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might have an impact on patient safety and data integrity to the Sponsor and to the IRB/EC in accordance with established IRB/EC policies and procedures. The Sponsor will review all protocol deviations and assess whether any represent a serious breach of Good Clinical Practice guidelines and require reporting to health authorities. As per the Sponsor's standard operating procedures, prospective requests to deviate from the protocol, including requests to waive protocol eligibility criteria, are not allowed.

14. CONDITIONS FOR TERMINATING THE STUDY

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Roche and the Investigator will assure that adequate consideration is given to the protection of the subjects' interests. The appropriate IRB/EC and Regulatory Agencies should be informed accordingly.

15. STUDY DOCUMENTATION, eCRFs AND RECORD KEEPING

15.1 Investigator's Files / Retention of Documents

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into 2 different separate categories [1] Investigator's Study File, and [2] subject clinical source documents.

The Investigator's Study File will contain the protocol/amendments, and schedule of assessments, Independent Ethics Committee/Institutional Review Board and governmental approval with correspondence, sample Informed Consent, drug records, staff curriculum vitae and authorization forms and other appropriate documents/correspondence, etc. In addition at the end of the study the Investigator will receive the subject data, which includes an audit trail containing a complete record of all changes to data, query resolution correspondence and reasons for changes, in human readable format on CD which also has to be kept with the Investigator's Study File.

Subject clinical source documents may include subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, ECG, signed ICFs, consultant letters, and subject screening and enrollment logs.

The Investigator must keep the 2 categories of documents as described above (including the archival CD) on file for at least 15 years after completion or discontinuation of the study. After that period of time the documents may be destroyed, subject to local regulations.

Should the Investigator wish to assign the study records to another party or move them to another location, Roche must be notified in advance.

If the Investigator cannot guarantee this archiving requirement at the investigational site for any or all of the documents, special arrangements must be made between the Investigator and Roche to store these in a sealed container[s] outside of the site so that they can be returned sealed to the Investigator in case of a regulatory audit. Where source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

ICH Good Clinical Practice guidelines require that Investigators maintain information in the study subject's records which corroborate data collected on the eCRF(s).

15.2 Source Documents and Background Data

The Investigator shall supply the Sponsor on request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

15.3 Audits and Inspections

The investigator should understand that source documents for this trial should be made available to appropriately qualified personnel from the Roche Pharma Development

Quality Assurance Unit or its designees or to health authority inspectors after appropriate notification. The verification of the eCRF data must be by direct inspection of source documents.

15.4 Electronic Case Report Forms

Data for this study will be captured via an EDC system. The data collected in the source documents is entered by the site onto the eCRFs. An audit trail will maintain a record of initial entries and changes made; reasons for change; time and date of entry; and user name of person performing entry or change.

For each subject enrolled, the eCRFs should be reviewed and electronically signed and dated by the principal investigator or authorized delegate from the study staff. This also applies to records for those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. If a subject is withdrawn from the study because of a treatment-limiting AE, thorough efforts should be made to clearly document the outcome.

The Investigator should ensure the accuracy, completeness and timeliness of the data reported to the sponsor in the eCRFs and in all required reports.

15.5 Financial Disclosure

The Investigator(s) will provide the Sponsor with sufficient accurate financial information (PD35) to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. The investigator is responsible to promptly update any information provided to the Sponsor if relevant changes occur in the course of the investigation and for 1 year following the completion of the study (last subject, last visit).

16. MONITORING THE STUDY

It is understood that the responsible Roche monitor [or designee] will contact and visit the Investigator regularly and will be allowed, on request, to inspect the various records of the trial [eCRFs and other pertinent data] provided that subject confidentiality is maintained in accord with local requirements.

It will be the monitor's responsibility to inspect the eCRFs at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. The monitor must verify that the subject received the study drug assigned by the randomization center (by controlling the written confirmation of the randomization by IVRS). The monitor should have access to all records needed to verify the entries on the eCRF. The Investigator [or deputy] agrees to cooperate with the monitor to ensure that any problems detected in the course of these monitoring visits are resolved.

Roche Clinical Repository specimens will at all times be tracked in a manner consistent with Good Clinical Practice, by a quality controlled, auditable and validated Laboratory Information Management System, to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in the study protocol and ICF, respectively. Roche monitors and auditors will have direct access to appropriate parts of

records relating to subjects participating in this study for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, Institutional Review Board/Independent Ethics Committee (IRB/IEC) review, and regulatory inspections by providing direct access to source data and documents related to the RCR Research Project.

17. CONFIDENTIALITY OF TRIAL DOCUMENTS AND SUBJECT RECORDS

The Investigator must assure that subjects' anonymity will be maintained and that their identities are protected from unauthorized parties. On eCRFs or other documents submitted to the Sponsor, subjects should not be identified by their names, but by an identification code. The Investigator should keep a subject enrollment log showing codes, names and addresses. The Investigator should maintain documents not for submission to Roche, e.g., subjects' written consent forms, in strict confidence.

Roche already maintains rigorous confidentiality standards for clinical studies by "coding" (i.e., assigning a unique patient identifier number at the Investigator site) all subjects enrolled in Roche clinical studies. This means that subject names are not included in data sets that are transmitted to any Roche location. Given the sensitive nature of genetic data, Roche has implemented a number of additional processes to assure subject confidentiality. All specimens taken for inherited genetic research that will be stored in the RCR (see 5.6.1) undergo a second level of "coding". At Roche, the specimen is transferred to a new tube and labeled with a new random number. This is referred to as "Double Coding (De-Identification)". Data generated following the use of these specimens and all clinical data transferred from the clinical database and considered relevant, will also be labeled with this same code. The "linking key" between the participant's identification number and this new independent code will be stored in a secure database system. Access to the table linking the participant identification number to the specimen code will be strictly limited and monitored by audit trail. Legitimate operational reasons for accessing the "linking key" will be documented in a standard operating procedure. Access to the "linking key" for any other reason will require written approval from the Governance Committee responsible for the specimen(s).

18. CLINICAL STUDY REPORT (CSR)

A CSR will be written and distributed to Health Authorities as required by applicable regulatory requirements. To fulfil the requirement of the EU Directive No 75/318/EEC the CSR will be signed by a coordinating Investigator who will be designated at a later stage.

19. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Roche will comply with the requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to Roche prior to submission. This allows the sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the Investigator.

In accordance with standard editorial and ethical practice, Roche will generally support publication of multicenter trials only in their entirety and not as individual center data. In this case, a coordinating Investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors (ICMJE) authorship requirements. Any formal publication of the study in which contribution of Roche personnel exceeded that of conventional monitoring will be considered as a joint publication by the investigator and the appropriate Roche personnel.

Data derived from RCR specimen analysis on individual subjects will not be provided to study Investigators, except where explicitly stipulated in a study protocol (e.g., if the result is an enrollment criterion). Exceptions may be granted (e.g., if biomarker data would be linked to safety issues). The aggregate results of any research conducted using RCR specimens will be available in accordance with the effective Roche policy on study data publication.

Any inventions and resulting patents, improvements and/or know- how originating from the use of the RCR will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2

A serious adverse event is any experience that suggests a significant hazard, contraindication, side effect or precaution. It is any AE that at any dose fulfills at least one of the following criteria:

- is fatal; [results in death] [NOTE: death is an outcome, not an event]
- is Life-Threatening [NOTE: the term "Life-Threatening" refers to an event in which the subject was at immediate risk of death at the time of the event; it does not refer to an event which could hypothetically have caused a death had it been more severe]
- requires in-subject hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is medically significant or requires intervention to prevent one or other of the outcomes listed above.

Medical and scientific judgment should be exercised in deciding whether expedited reporting to the sponsor is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definitions above. These situations should also usually be considered serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

An unexpected AE is one in which the nature or severity is not consistent with the applicable product information.

Causality is initially assessed by the Investigator. For Serious Adverse Events, possible causes of the event is indicated by selecting one or more options. (Check all that apply)

- Pre-existing/Underlying disease - specify
- Study treatment - specify the drug(s) related to the event
- Other treatment (concomitant or previous) - specify
- Protocol-related procedure
- Other (e.g., accident, new or intercurrent illness) – specify

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 [Cont.]

The term severe is a measure of intensity, thus a severe AE is not necessarily serious. For example, nausea of several hours' duration may be rated as severe, but may not be clinically serious.

A serious adverse event occurring during the study or which comes to the attention of the Investigator within 15 days after stopping the treatment or during the protocol-defined follow-up period, if this is longer, whether considered treatment-related or not, must be reported. In addition, a serious adverse event that occurs after this time, if considered related to test "drug", should be reported.

Such preliminary reports will be followed by detailed descriptions later which will include copies of hospital case reports, autopsy reports and other documents when requested and applicable.

For serious adverse events, the following must be assessed and recorded on the AEs eform of the eCRF: intensity, relationship to test substance, action taken, and outcome to date.

The Investigator must notify the Ethics Review Committee/Institutional Review Board of a serious adverse event in writing as soon as is practical and in accordance with international and local laws and regulations.

ROCHE LOCAL COUNTRY CONTACT for SAEs: Local Monitor:

See attached *Protocol Administrative and Contact Information & List of Investigators Form, [gcp_for000227]*, for details of administrative and contact information.

ROCHE HEADQUARTERS CONTACT for SAEs and other medical emergencies: Clinical Operations/Clinical Science:

See attached *Protocol Administrative and Contact Information & List of Investigators form, [gcp_for000227]*, for details of administrative and contact information.

24 HOUR MEDICAL COVERAGE:

Identification of a contact for 24 Hour Medical Coverage is mandatory to be compliant with worldwide regulatory agencies and to ensure the safety of study subjects.

An Emergency Medical Call Center Help Desk will access the Roche Medical Emergency List, escalate emergency medical calls, provide medical translation service (if necessary), connect the Investigator with the Roche medical contact for this study and track all calls. The Emergency Medical Call Center Help Desk will be manned 24 hours 7 days a week. Toll free numbers will be distributed to all Investigators running Roche Pharma Development clinical trials. The Help Desk will be used for medical emergencies outside regular business hours, or when the regular Clinical Science Leader/Clinical Pharmacology Leader cannot be reached.

Appendix 1 ICH Guidelines for Clinical Safety Data Management, Definitions and Standards for Expedited Reporting, Topic E2 [Cont.]

See the attached *Protocol Administrative and Contact Information & List of Investigators form [gcp_for000227]*, for details of administrative, contact information, and Emergency Medical Call Center Help Desk toll-free numbers.

Appendix 2 CANTAB – Descriptions of tests used in this study

Motor Screening Test (MOT)

The Motor Screening test is a training procedure designed to introduce the subject to the computer and touch screen. It should always be given at the beginning of a session. It simultaneously screens for difficulties with vision, movement and comprehension and ascertains that the subject can follow simple instructions.

A series of crosses is shown in different locations on the screen. The rater demonstrates with the first 3 crosses, the correct way to point using the forefinger of their dominant hand, then the subject must touch the next set of crosses in turn.

Test duration: approximately 3 minutes

Reaction Time (RTI)

Reaction Time (RTI) is a latency task with a comparative history (the 5 choice task) and uses a procedure to separate response latency from movement time. It is more useful than CRT or SRT where it is necessary to control for tremor.

The task is divided into 5 stages, which require increasingly complex chains of responses. In each case, the subject must react as soon as a yellow dot appears. In some stages the dot may appear in 1 of 5 locations, and the subject must sometimes respond by using the press-pad, sometimes by touching the screen, and sometimes both.

The four outcome measures in RTI are divided into reaction time (simple and 5-choice) and movement time (simple and five-choice).

Test duration: approximately 5 minutes

Pattern Recognition Memory ([PRM] Immediate and Delayed)

This is a test of visual pattern recognition memory in a 2-choice forced discrimination paradigm. The subject is presented with a series of 12 visual patterns, one at a time, in the center of the screen. These patterns are designed so that they cannot easily be given verbal labels. In the recognition phase, the subject is required to choose between a pattern they have already seen and a novel pattern. In this phase, the test patterns are presented in the reverse order to the original order of presentation. This is then repeated, with 12 new patterns. The second recognition phase can be given either immediately or after a 20 minute delay.

Test duration: approximately 5 minutes

Delayed Match to Sample (DMS)

DMS is a test of simultaneous and delayed matching to sample. This test is primarily sensitive to damage in the medial temporal lobe area, with some input from the frontal lobes.

The subject is shown a complex visual pattern (the sample) and then, after a brief delay, 4 patterns. Each pattern is made up of 4 sub-elements, each of a different colour.

The subject is instructed to touch the pattern that matches the sample. In some trials the sample and the choice patterns are shown simultaneously, whereas in others a delay (of 0, 4, or 12 seconds) is introduced between covering the sample pattern and showing the choice patterns. If the first choice is incorrect, the subject must make a second choice, and so on, until a correct choice is made.

Test duration: approximately 7 minutes

Spatial Working Memory (SWM)

This is a test of the subject's ability to retain spatial information and to manipulate remembered items in working memory. This test is a sensitive measure of frontal lobe and executive dysfunction.

The test begins with a number of coloured squares (boxes) being shown on the screen.

The subject must touch each box in turn until one opens with a blue token. When a blue token has been found, the subject has to place it in the black column ('home') by touching the right-hand side of the screen. The subject must then begin a new search for the next blue token. It may be in any of the boxes that so far have been empty. This is repeated, until a blue token has been found in every box on the current screen. Touching any box in which a blue token has already been found is an error. The test consists of stages which increase in difficulty according to the number of boxes that must be opened.

Test duration: approximately 8 minutes

Rapid Visual Information Processing (RVP)

This test is sensitive to dysfunction in the parietal and frontal lobe areas of the brain and is also a sensitive measure of general performance.

RVP is a test of visual sustained attention. A white box appears in the centre of the computer screen, inside which digits, from 2 to 9, appear in a pseudo-random order, at the rate of 100 digits per minute. The test is in 2 parts; a 'warm-up' practice stage which lasts for 2 minutes and is not scored, and a test stage which lasts for 7 minutes.

Subjects are requested to detect target sequences of digits (for example, 2-4-6, 3-5-7, 4-6-8) and to register responses by touching the screen.

Test duration: approximately 9 minutes

Paired Associates Learning (PAL)

The PAL test assesses visual memory and new learning. This test is primarily sensitive to changes in medial temporal lobe functioning.

Boxes are displayed on the screen. All are opened in a randomised order. One or more of them will contain a pattern. The patterns shown in the boxes are then displayed in the middle of the screen, one at a time, and the subject must touch the box where the pattern was originally located.

Appendix 2 CANTAB – Descriptions of tests used in this study (Cont.)

The test consists of stages which increase in difficulty during the test as more patterns are hidden in the boxes. If an error is made the patterns are re-presented to remind the subject of their locations. At each stage the subject may have up to 6 attempts in total (the first presentation of all the shapes, then up to 5 repeat presentations). When the subject gets all the locations correct, they proceed to the next stage. If the subject cannot complete a stage correctly, the test terminates.

Test duration: approximately 10 minutes