Official Title: A Phase III, Randomized, Double-Blind,Placebo-Controlled, Parallel-Group, Multicenter, Efficacy and Safety Study of Gantenerumab in Patients With Mild Alzheimer's Disease; Part II: Open-Label Extension for Participating Patients

NCT Number: NCT02051608

Document Date: Protocol Version 5: 28-February-2020

PROTOCOL

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER, EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH MILD ALZHEIMER'S DISEASE; PART II: OPEN-LABEL EXTENSION FOR PARTICIPATING PATIENTS**
PROTOCOL NUMBER:	WN28745
VERSION NUMBER:	5
EUDRACT NUMBER:	2013-003390-95
IND NUMBER:	102266
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted] M.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
DATE FINAL:	Version 1: 15 November 2013
DATES AMENDED:	Version 2: 28 October 2014 Version 3: 27 October 2015 Version 4: 2 December 2017 Version 5: See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
28-Feb-2020 12:16:52	Company Signatory	[redacted]

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

Protocol WN28745 has been amended for two main reasons: 1) to allow patients who complete dosing visits in Study WN28745 to enroll in an open-label rollover (OLE) study (WN41874) without any unnecessary dosing gap, and 2) to enable the use of leftover plasma samples, collected for pharmacokinetic (PK) and anti-drug antibody (ADA) analysis, for exploratory biomarker research. Changes to the protocol, along with a rationale for each change, are summarized below:

- The background on gantenerumab has been updated with current information about past and ongoing studies (Sections 1.3 and 1.4.8).
- Language has been modified to clarify that amyloid-related imaging abnormalities (both edema/effusion and hemosiderin depositions) and injection-site reactions are identified risks for gantenerumab (Sections 1.3.3 and 5.1).
- Language has been added to enable patients to enroll in Study WN41874 (open-label rollover study) to continue to receive gantenerumab for 2 more years. Patients who enroll in Study WN41874 will not undergo follow-up assessments 16 weeks after their last dose (Follow–Up 2 visit) (Sections 3.1.2, 3.2, 3.4.2.1, 4.3.4, 4.6.3.1, 4.6.3.3, 4.6.3.4, 5.3.1, and 5.6 and Appendix 2).
- Positron emission tomography tracers used in the substudies associated in this substudy are included as investigational medicinal products (IMPs) or non-IMPs. Section 4.3.2.5 has been added.
- Language has been added to enable the use of leftover plasma samples, collected for PK and ADA analysis, for exploratory biomarker research (Sections 4.5.8, 4.5.11, and 4.5.14.1).
- Language has been modified to clarify the timing of follow-up visits for Part 1 versus Part 2 (Sections 4.6.3.3, 4.7.2, 5.3.1, and 5.6).
- Information about the potential for development of anti-drug antibodies has been added for consistency with the most recent Gantenerumab Investigator's Brochure (Sections 5.1.2 and 5.1.3).
- Medical Monitor contact information has been modified (Section 5.4.1).
- Documents to be used for reference safety information for the PET tracers have been specified (Section 5.7).
- Language regarding ICF amendments has been updated as per new standard Sponsor language (Section 8.2).
- Appendix 2 has been corrected to clarify that treatment is not to be administered at the Follow-Up 1 visit.
- An optional lumbar puncture at Week 104 has been added to the schedule of assessments for all patients (Table 5, Appendix 2).

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:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER, EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH MILD ALZHEIMER'S DISEASE; PART II: OPEN-LABEL EXTENSION FOR PARTICIPATING PATIENTS**
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MEDICAL MONITOR:	[redacted], M.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 return the signed original of this form as instructed by your local study monitor.
Please retain a copy for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, MULTICENTER, EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH MILD ALZHEIMER'S DISEASE; PART II: OPEN-LABEL EXTENSION FOR PARTICIPATING PATIENTS**
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VERSION NUMBER:	5
EUDRACT NUMBER:	2013-003390-95
IND NUMBER:	102266
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Part 1 Objectives

Efficacy Objectives

The primary efficacy objective of this study was to evaluate the efficacy of gantenerumab compared with placebo administered to patients by subcutaneous (SC) injection over 100 weeks as measured by the following co-primary endpoints (final outcome assessment 4 weeks after the final dose):

- Cognition, as measured by the Alzheimer's Disease Activity Scale–Cognitive (ADAS-Cog) (13-item)
- Function, as assessed by the Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL)

The key secondary efficacy objectives for this study was to evaluate the benefits of gantenerumab versus placebo administered to patients by SC injection over 100 weeks on slowing clinical decline and disease progression by assessing the following key secondary endpoint domains:

- Time to clinically evident decline, as determined by:
  - Confirmed decline of ≥2 points (at two consecutive visits) on the Mini Mental State Examination (MMSE), and
  - Loss of ≥1 points on one or more basic ADL, as measured on the ADCS-ADL or
  - Loss of ≥2 points on one or more instrumental activities of daily living (IADL), as measured on the ADCS-ADL
- Change from baseline at Week 104 in Clinical Dementia Rating-Sum of Boxes (CDR-SB)
- ADAS-Cog responder(see the Statistical Analysis Plan for more details)

- The disease pathology biomarkers:

  Effect of gantenerumab on cerebral spinal fluid (CSF) biomarkers reflecting Alzheimer's disease (AD) pathology (i.e., amyloid-beta [Aβ]1–42, total tau [t-tau] and phosphorylated tau [p-tau])

  Effect of gantenerumab on neurodegeneration, measured using structural (whole brain and regional brain atrophy) magnetic resonance imaging (MRI) before, during, and after treatment

The following additional secondary endpoints and their respective domains were to be evaluated:

- Global

  Effect on severity of dementia, assessed using the Clinical Dementia Rating–Global score (CDR-GS)

- Cognition

  Effect on cognition, assessed using the MMSE

  Effect on cognition assessed with the ADAS-Cog13 using a responder analysis, for which response is defined as an increase of ≤ 4 points on the ADAS-Cog13 from baseline (i.e., worsening)

- Behavior

  Effect on behavioral and neuropsychological symptoms of AD, assessed using the Neuropsychiatric Inventory (NPI)

Other AD symptoms and effects

- Effect of gantenerumab on health-related quality of life (QoL), assessed using the Quality of Life–AD (QoL-AD) scale
- Effect of gantenerumab on patient-individualized goal achievement using the SymptomGuide™ Facilitated Goal Attainment Scaling (GAS; to be conducted at sites in English and French speaking countries only)
- Effect of gantenerumab on caregiver emotional well-being using the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale
- Effect of gantenerumab on the amount of assistance patients with dementia require in performing daily activities, using the Dependence Scale (DS) and Resource Utilization Dementia–Lite (RUD-Lite)

Safety Objectives

The safety objectives for this study were as follows:

- To evaluate the safety of gantenerumab compared with placebo in patients with mild AD, focusing on physical and neurologic examinations, vital signs, blood safety tests, electrocardiograms (ECGs), and adverse event monitoring
- To evaluate the safety of gantenerumab compared with placebo in patients with mild AD, focusing on adverse events as assessed on MRI:

  Amyloid-related imaging abnormalities–edema/effusion (ARIA-E)

  Amyloid-related imaging abnormalities–hemosiderin depositions (ARIA-H)

- The development of anti-gantenerumab antibodies, referred to as anti-drug antibodies (ADAs) (also known as human anti–human antibodies)

  The development of ADAs will be assessed, and if detected, whether there is an association with the pharmacokinetic (PK), pharmacodynamic (PD), efficacy, and safety parameters following treatment with gantenerumab.

Pharmacodynamic Objectives

The PD objective of this study was as follows:

- To assess changes in amyloid load in the brain and heart over time using a florbetapir F 18 injection (Amyvid™), a positron emission tomography (PET) radioligand selective to β-amyloid, in patients with mild AD (as determined by clinical criteria and Aβ CSF) who are treated with gantenerumab or placebo.

The PD objective will be evaluated in a subset of consenting patients (approximately 60 patients in the PET substudy assessing brain amyloid, 5 of whom also participated in the cardiac PET substudy). Details of the substudies are described in separate protocols (WN28745-PET and WN28745-Cardiac PET).

Pharmacokinetic Objectives

The PK objective for this study was as follows:

- To explore the pharmacokinetics of gantenerumab in patients with mild AD and the influence of covariates on the PK behavior.

Exploratory Objectives

The exploratory objective for this study was as follows:

- To evaluate if the removal of Aβ by gantenerumab in the brains of patients with mild AD will modulate functional brain connectivity (i.e., increase brain functional connectivity using resting state functional magnetic resonance imaging [rs-fMRI]) compared with patients treated with placebo

Exploratory biomarkers will be assessed in consenting patients.

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biologic specimens. Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. Specimens stored in the RCR will be used to:

- Study the association of biomarkers with efficacy and/or adverse events associated with the medicinal product
- Increase our knowledge and understanding of disease biology
- Study drug response, including drug effects and the processes of drug absorption and disposition
- Develop biomarker or diagnostic assays and establish the performance characteristics of these assays

Part 2 Objectives

The main objective of the OLE is to evaluate the safety and tolerability of gantenerumab at higher doses focusing on physical and neurologic examinations, vital signs, blood safety tests, ECGs, and adverse event monitoring. All patients previously enrolled and ongoing in the study will be eligible to receive active gantenerumab and will be up titrated gradually to the highest possible dose up to 1200 mg.

The secondary objectives will include the following:

- To evaluate the effect of higher doses of gantenerumab on imaging biomarkers (PET and MRI) on CSF biomarkers and on clinical outcome measures (cognition and function) over time
- To explore pharmacokinetics at the higher gantenerumab doses

Efficacy Outcome Measures in Part 1

The co-primary efficacy measures for Part 1 of this study were as follows:

- Mean change from baseline at Week 104 in ADAS-Cog13
- Mean change from baseline at Week 104 in ADCS-ADL score

The key secondary efficacy measures for Part 1 of this study were the following:

- Time to clinical decline as measured by
  - Confirmed (at two consecutive visits) ≥2-point decline on MMSE, and
  - Loss of ≥1 points on one or more basic ADL, as assessed with the ADCS-ADL or
  - Loss of ≥2 points on one or more IADL, as assessed with the ADCS-ADL
- Change from baseline at Week 104 in CDR-SB
- ADAS-Cog responder (see the Statistical Analysis Plan for more details)
- Change from baseline (i.e., collected at screening) to Week 104 in CSF t-tau, p-tau, and Aβ1–42 levels

The secondary biomarker outcome measures for this study were as follows:

- Change from baseline (screening visit) to Week 104 in CSF t-tau, p-tau, and Aβ1–42 levels
- Change from baseline (screening visit) to Week 104 in MRI volumetry, as assessed on structural MRI:
  - Change from baseline in hippocampal volume
  - Change from baseline in whole brain volume
  - Change from baseline in cortical thickness
  - Change in baseline in ventricular volume
- Changes in brain and heart amyloid load over time using a florbetapir F 18 injection, a PET radioligand selective to β-amyloid in patients treated with gantenerumab or placebo

Additional secondary efficacy outcome measures for Part 1 of this study were the mean change from baseline at Week 104 in the following:

- CDR-GS
- ADAS-Cog13 scores
- NPI total and domain scores (neuropsychiatric behavior)
- MMSE total score (cognition)
- Clinical composite endpoint (prespecified items from the ADAS-Cog, MMSE, and CDR)
- QoL-AD (global score)
- SymptomGuide™ Facilitated GAS (change in symptoms and goal achievement)
- DS (global score, and Cognitive Support and Assistance and Elder Active scales)
- RUD-Lite (resource utilization, time care-giving, caregiver productivity, and institutionalization)
- ZCI-AD (domains and global scores)

Efficacy Measures in Part 2

During the First Two Years

Efficacy measures in Part 2 are exploratory and will include both clinical outcome measures (ADAS-Cog, MMSE, CDR, and ADCS-ADL) and biomarker measures.

During the Additional Years

Only the MMSE will be collected during the additional years.

Safety Outcome Measures in Parts 1 and 2

The safety outcome measures for this study are as follows:

- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of treatment discontinuations due to adverse events

- Mean changes in clinical laboratory tests from baseline over time and incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Incidence of anti-gantenerumab antibodies
- Physical and neurologic examination abnormalities
- Mean change in vital signs assessment from baseline over time and incidence of abnormal vital signs measurements
- Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, as determined using the Columbia–Suicide Severity Rating Scale (C-SSRS)

Pharmacokinetic Outcome Measures in Parts 1 and 2

The PK outcome measures for this study are as follows:

- Primary population PK parameters (e.g., apparent total CL [CL/F] and apparent volume of distribution [V/F]) and relevant covariates as necessary to describe the plasma gantenerumab concentration–time course
- Secondary population estimates of plasma gantenerumab exposure at steady state to include peak plasma concentration (C_{max}), time to peak concentration (T_{max}), trough plasma concentration (C_{min}), and AUC

Exploratory Outcome Measures in Parts 1 and 2

The exploratory outcome measures for this study are as follows:

- Change from baseline (screening visit) to Week 104 in functional brain connectivity as measured by rs-MRI

Study Design

Description of Study in Part 1

Study WN28745 was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of gantenerumab in patients with mild AD. Patients with mild AD were selected on the basis of clinical diagnosis of probable mild AD according to the National Institute of Neurological and Communicative Disorders and Stroke/ Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA) criteria or probable neurocognitive disorder (NCD) due to AD, mild severity using the Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5) criteria, and biomarker evidence for increased amyloid burden.

Description of Study in Part 2

All patients (299 patients) who are actively enrolled in Study WN28745 (i.e., not discontinued from study drug) were invited to participate in the OLE study.

Patients will receive open-label gantenerumab by SC injection q4w for up to an additional 3 years beyond the initial 2 years of OLE, followed by a safety and limited efficacy assessment 4 weeks following the last dose (Follow-Up 1 visit; see schedule of assessments). *The first dose of open-label gantenerumab will be administered after the patient has signed the OLE informed consent form (ICF). Patients will then be given the option of enrolling in an open-label rollover study (WN41874) aimed at evaluating the safety and tolerability of long-term administration of gantenerumab.* Patients *who do not enroll in Study WN41874* will have one additional follow-up visit: Follow-Up 2 at 16 weeks after the final dose for safety and limited efficacy.

In addition to the initial 2 years in OLE, patients will be given the option to continue receiving open-label gantenerumab treatment until the end of end of 2020. Patients who discontinue study drug at any time during OLE, or who complete the first 2 years of OLE only will be asked to complete follow-up visits at 4 and 16 weeks from their last dose (Follow-Up 1 and 2, respectively).

Number of Patients

The planned number of patients was approximately 1000 (500 randomized to gantenerumab and 500 to placebo). Patients were assigned to receive gantenerumab or placebo in a 1:1 ratio. Randomization was stratified by geographic region, APOE ε4 status, and use or non-use of anti-dementia medications at baseline in order to maintain a balanced number of patients in each of these strata enrolled in each treatment arm. Approximately 225 centers in approximately 30 countries were to participate.

Three hundred eighty nine patients were enrolled in Part 1 of the study. Patients still actively enrolled in Study WN28745 (i.e., not discontinued from study drug during Part 1) were invited to participate in the OLE study.

Target Population

Patients were eligible for study participation whether or not they were receiving approved symptomatic medications for AD (i.e., cholinesterase inhibitors [ChEIs] or memantine; or the medical food supplement Souvenaid®, where approved). Eligible patients were 50−90 years old and at the time of screening, had an MMSE score of 20–26 points, inclusive, a GDS-15 (Geriatric Depression Scale) score < 6, and a CDR-GS of 0.5 or 1.0. Patients also had increased brain amyloid, as measured by reduced CSF Aβ1–42. Neuroradiologic evaluation using a standard MRI protocol and T_2*-weighted gradient-recalled echo (GRE) fluid attenuated inversion recovery MRI as read by the central MRI reader was used to exclude patients with other structural causes of dementia, significant cerebral vascular pathology, more than four microbleeds, and areas of leptomeningeal hemosiderosis combined on a 1.5-Tesla (T) MRI scanner or more than five microbleeds on a 3–T MRI scanner, or evidence of a prior cerebral macrohemorrhage.

Inclusion Criteria in Part 1

Patients must have met the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee [IEC] or institutional review board [IRB])
- Ages 50–90 years, inclusive
- Clinical diagnosis of probable mild AD based on NINCDS/ADRDA criteria or major NCD due to AD of mild severity based on the DSM-5 criteria whether or not receiving AD approved medication
- If the patient is receiving AD medications, the dosing regimen must have been stable for 3 months prior to screening
- Males and females
- For females 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 or urine tests will be performed for further confirmation of non-childbearing potential if required by local regulations, guidelines, and IEC/IRB
  or
  For females of childbearing potential, a negative urine beta-human chorionic gonadotropin (β-hCG) will be required at screening and baseline, and agreement to use two acceptable forms of effective contraception from the screening visit until 16 weeks after study drug discontinuation as follows:

  Established use of oral, injected, or implanted hormonal methods of contraception

  Intrauterine system or placement of an intrauterine device

  Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository

  Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)

  True abstinence: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception

- Availability of a person ("caregiver") who in the investigator's judgment has frequent and sufficient contact with the patient (e.g., ≥ 10 hours per week of in-person contact), is able to provide accurate information regarding the patient's cognitive and functional abilities, agrees to provide information at clinic visits, which requires partner input for scale completion, and signs the necessary consent form

  The caregiver must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the patient's behavior and cognitive and functional abilities. Whenever possible, the caregiver should be the same for the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture, clinical genotyping, and PET imaging if applicable); the patient should be capable of completing assessments either alone or with the help of the caregiver
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies

Cognition-Related and Test-Based Criteria for Mild Alzheimer's Disease

- Screening MMSE score of 20–26 points, inclusive, at screening
- Screening CDR-GS of 0.5–1.0
- Screening GDS-15 score < 6
- CSF Aβ1–42 levels ≤ 700 pg/mL as measured on the Elecsys assay

Exclusion Criteria in Part 1

Patients who met any of the following criteria were excluded from study entry:

Central Nervous System Disorders

- Dementia or NCD due to a condition other than AD, including, but not limited to, frontotemporal dementia, Parkinson disease, dementia with Lewy bodies, Huntington disease, or vascular dementia
- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., clinically significant carotid or vertebral stenosis or plaque, aortic aneurysm, intracranial aneurysm, cerebral hemorrhage, arteriovenous malformation) that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of stroke within the past 2 years or documented history of transient ischemic attack within the last 12 months
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) central nervous system (CNS) trauma (e.g., cerebral contusion)
- History or presence of clinically relevant intracranial tumor (e.g., glioma, cerebral metastasis) that is clinically relevant in the opinion of the investigator
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis, human immunodeficiency virus [HIV], encephalopathy)
- History or presence of systemic autoimmune disorders potentially causing progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease)

- History or presence of a neurologic disease other than AD that may affect cognition, including, but not limited to, Parkinson disease, corticobasal degeneration, dementia with Lewy bodies, Creutzfeldt–Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, and hypoxia
- History of schizophrenia, schizoaffective disorder, or bipolar disorder
- At risk of suicide in the opinion of the investigator
- Alcohol and/or substance use disorder (according to the DSM-5) within the past 2 years (nicotine use is allowed)

Imaging-Related Criteria

- According to the assessment by the central reader, magnetic resonance imaging (MRI) evidence of a) more than two lacunar infarcts, b) any territorial infarct >1 cm^3, or c) any white matter lesion corresponding to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid attenuated inversion recovery (FLAIR) sequence, which is ≥ 20 mm in any dimension
- The combined number of microbleeds and areas of leptomeningeal hemosiderosis on MRI is more than four on a 1.5-T machine or more than five on a 3-T machine based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

Cardiovascular Disorders

- History or presence of atrial fibrillation (except if only one episode, which resolved more than 1 year ago and for which treatment is no longer indicated), or cardiovascular disorder that in the investigator's judgment poses a risk for future stroke
- Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, cardiac failure New York Heart Association Class II or higher)
- Uncontrolled hypertension (e.g., blood pressure [BP] generally >160 mm/Hg systolic or >95 mmHg diastolic)

Hepatic/Renal Disorders

- Chronic kidney disease as indicated by creatinine clearance <30 mL/min as calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Impaired hepatic function as indicated by screening AST or ALT $\geq 2\times$ or total bilirubin $\geq 1.5\times$ the upper limit of normal (ULN), which remains above these limits if retested due to a slightly elevated initial result, or abnormalities in synthetic function tests that are judged by the investigator to be clinically significant

Infections and Immune Disorders

- History of or known to currently have HIV infection, hepatitis B or C infection not adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

Metabolic and Endocrine Disorders

- Abnormal screening thyroid function tests such that a new treatment or an adjustment of current treatment is required

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for thyroid function.
- Screening folic acid or vitamin B12 levels that are sufficiently low and remain low on retest such that deficiency may be contributing to cognitive impairment, or such that the deficiency requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment.
- Screening hemoglobin A_{1c} (HbA_{1C}) > 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes).

  The patient may be rescreened after 3 months to allow optimization of diabetic control.

Other Exclusions

- Intellectual disability (static encephalopathy, closed brain injury, mental retardation) that has been excluded by the investigator:

  This may be based on, for example, patient's sufficient education or work experience.
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture
- Clinically significant abnormal screening blood, urine, or CSF that remain abnormal on retest
- Screening prothrombin time (PT) > 1.2 × the ULN
- History of cancer except:

  If considered to be cured

  If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, not likely to require treatment in the ensuing 5 years

  For prostate or basal cell carcinoma, no significant progression over the last 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab's excipients
- Any other severe or unstable medical condition not previously mentioned that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility. Patients who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a caregiver who meets the minimum requirement.

Medication-Related Criteria

The following medications are prohibited for a prespecified duration prior to study start, as indicated, and during the entire period of study participation (patients who start these medications during the study will be withdrawn):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any investigational passive immunotherapy (vaccine) or other long-acting biologic agent that is being evaluated to prevent or postpone cognitive decline within 1 year of screening

- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 3 months of screening, whichever is longer
- Any previous treatment with medications used to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening even if the patient is taking the medicine for a non-neurodegenerative disorder such as restless leg disorder
- Typical antipsychotic or a neuroleptic medication within 6 months of screening except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Antihemostasis medications within 3months of screening except for:

  Daily use of aspirin (up to 100 mg/day) or clopidogrel are permitted if stable for the previous 3 months
- Systemic immunosuppressive therapy including corticosteroids within 3 months of screening or anticipated to be needed during the study
- Chronic narcotic analgesics within 6 months of screening
- Stimulant medications (eg., amphetamine, methylphenidate preparations) within 1 month of screening
- Anticonvulsant medications within 1 month of screening
- Sedative, hypnotic, or benzodiazepine medication within 3 months of screening, except intermittent use of the following for sleep or anxiety:

  Alprazolam, lorazepam, oxazepam, temazepam, diazepam

  A short-acting benzodiazepine-like medication (e.g., zolpidem)

The intermittent use of these medications is permitted, but there should be no use for 4 days prior to any cognitive assessments.

The following medications are permitted if the dose and dose regimen have been stable for 1 month prior to screening (approximately 3 months prior to randomization) and are expected to remain stable after randomization:

- Prescription medications that might affect cognitive function (e.g., antidepressants, atypical antipsychotic medications
- Over-the-counter and/or herbal medications, food additive or any other agent or supplement intended to improve cognition or reduce cognitive decline, including, but not limited to, Alzhemed®, ginkgo biloba, huperzine, lecithin, and vitamin B12
- Medications used to treat a mood or anxiety disorder, including selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, bupropion, buspirone, mirtazapine, or trazodone, given as maintenance treatment
- Medications with anticholinergic activity that may impair cognition or attention (e.g., centrally acting antihistamines, including brompheniramine, chlorpheniramine, dimenhydrinate, diphenhydramine, and doxylamine, or antispasmodic medicines).

  Intermittent use of centrally acting antihistamines is permitted, but there should be no use for 4 days prior to any cognitive assessments.

Eligibility Criteria in Part 2 (OLE):

All patients who have been randomized and are actively participating in the study at the time of the amendment approval in their respective country will be eligible to participate in the OLE. Patients who have been discontinued from the study will not be allowed to enroll in the OLE.

Patients in the OLE will be given the option of extending open-label treatment beyond the initial 2 years.

End of Study

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date on which the last datapoint required for safety follow-up is received from the last patient in the OLE. The LPLV is expected to occur *4 or 16 weeks (as applicable)* after the last patient has received their last dose of study drug (i.e., Follow-Up *1 or* 2 visit).

Length of Study

During Part 1, the study consisted of a screening period of up to 8 weeks in length for each eligible patient who signs the informed consent and agrees to participate, followed by a double-blind treatment period of 100 weeks and a 52-week follow-up period. In OLE, the study will consist of open-label treatment until the end of 2020 and a *4- or 16-week* follow-up period.

Investigational Medicinal Products

Test Product

In Part 2, open-label gantenerumab will be administered by SC injection to all patients with APOE ε4 status (0ε4 'non-carriers' and 1ε4/2ε4 'carriers') with previous dose assignment defining the titration rate to the target dose of 1200 mg every 4 weeks (q4w). Patients with non-carrier status previously on 225 mg gantenerumab will receive a dose of 600 mg q4w for the first 2 doses, followed by 1200 mg q4w thereafter to the end of the study. Patients with non-carrier status previously on placebo or 105 mg gantenerumab will receive a starting dose of 300 mg q4w for the first 2 doses followed by 600 mg q4w for 2 doses, then 1200 mg q4w thereafter to the end of the study.

Patients with carrier status previously on 225 mg gantenerumab will receive a dose of 450 mg q4w for 2 doses, 900 mg q4w for 2 doses, and 1200 mg q4w thereafter to the end of the study. Patients with carrier status previously on placebo or 105 mg gantenerumab will receive a dose of 225 mg q4w for 2 doses, 450 mg q4w for 2 doses, 900 mg q4w for 2 doses, and 1200 mg q4w thereafter to the end of the study. Central MRI results as detailed in Section 5.1.3 will be required prior to every dose increase.

On study drug administration days that include efficacy assessments, study drug must be administered at the clinical site. Study personnel administering study drug must not be involved with any study procedures.

At select sites, on days when only safety is being assessed, there is an option to have study drug administered and applicable safety assessments conducted at a prearranged location away from the study site by a trained health care provider if consent is obtained.

Non-Investigational Medicinal Products

Stable (≥ 3 months prior to screening and approximately 5 months prior to randomization) dose and dose regimen of approved medications for AD will be permitted at study entry. Dose, dose regimen, and dosing status at entry (i.e., receiving or not receiving) should remain stable. Stable doses of other maintenance medications will also be permitted if not prohibited per the entry criteria. Patients must have been on stable doses of any prescription medications that might affect cognitive function for 1 month prior to screening (approximately 3 months prior to randomization).

During the study, patients will be permitted to receive any treatment deemed necessary by the investigator for the management of their disease. However, patients requiring initiation of excluded therapies must discontinue from the study. (Note: Patients who are not receiving anti-dementia medications at study entry and subsequently require such treatments at least 6 months after randomization will be permitted to continue on their randomized treatment and be followed for efficacy and safety assessments.)

In Part 2, patients will be permitted to receive any treatment deemed necessary by the investigator for the management of their disease. As much as possible, medications should be chosen from the list of permitted medications.

Statistical Methods

Primary Analysis

The primary analysis population for all efficacy analyses was the intent-to-treat (ITT) analysis population. The ITT population would have included all randomized patients who receive at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

The co-primary efficacy endpoints were the absolute change from baseline to the end of Week 104 in ADAS-Cog13 and ADCS-ADL.

For each of the primary endpoints, the null and alternative hypotheses to be tested were:

$$H_0: \mu = 0 \text{ versus } H_A: \mu \neq 0$$

for which μ is the assumed treatment difference in the absolute change from baseline in the endpoint between the gantenerumab and placebo groups. For each endpoint, the null hypothesis of no treatment difference will be rejected if the two-sided p-value is ≤ 0.05.

The primary efficacy analyses were to include all randomized patients, with patients grouped according to the treatment assigned at randomization.

For the assessment of difference between the gantenerumab group and placebo with regard to the mean change from baseline in each primary endpoint at the end of Week 104, a mixed-effects model repeated measures (MMRM) analysis, incorporating data up to 104 weeks of treatment, was to be used to utilize all the data collected over time. For the primary efficacy analyses, all observations recorded after any modification of the patient's baseline AD medication regimen (change in the dose of the medication or initiation of a new medication) were to be excluded.

For each co-primary endpoint, the model would have included the absolute change from baseline in the endpoint as the dependent variable. The effects in the model would have included independent variables of treatment, assessment weeks relative to the first dose of study drug (i.e., time), treatment-by-time interaction, APOE ε4 status (carrier versus non-carrier), baseline AD medication (either receiving AD treatment or not), and the respective baseline value as covariate. An unstructured variance-covariance structure was to be applied to model the within-patient errors and to enable the inclusion of data from patients with incomplete data across scheduled timepoints.

In order to assess the effect of missing data on the analysis results for the co-primary and key secondary endpoints, sensitivity analyses were to be performed using multiple imputation methods and pattern mixture models. Sensitivity analyses were also to be performed in which observations recorded after any modification of a patient's baseline AD medication regimen would be included.

Additional details will be documented in the Statistical Analysis Plan.

Secondary Analyses

The absolute change from baseline in the continuous secondary efficacy endpoints listed (including cognitive endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) was to be analyzed using an MMRM analysis model as described above for the primary efficacy endpoint.

The time to first occurrence of the key secondary endpoint of time to clinical decline was to be analyzed using a stratified proportional hazards model, with APOE ε4 genotype as a stratification factor.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the co-primary endpoints and these key secondary endpoints into the analysis, the hierarchical testing procedure in the protocol was specified as follows.

Step 1a: Test the change from baseline in ADAS-Cog (a co-primary efficacy endpoint) comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

Step 1b: Test the change from baseline in ADCS-ADL (a co-primary efficacy endpoint) comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

The result of Step 1 of the testing procedure is considered statistically significant only if the p-values for both Steps 1a and 1b (i.e., both co-primary efficacy endpoints) are statistically significant at $\alpha = 0.05$. If either p-value is > 0.05, the result of Step 1 is considered non-significant and no further testing will be performed.

If Step 1a **and** Step 1b are significant, continue testing.

↓

Step 2: Test the time to first occurrence of clinical decline between the gantenerumab and placebo arms at $\alpha = 0.05$.

If Step 2 is significant,

↓

Step 3: Test the change from baseline in CDR-SB comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

If Step 3 is significant,

↓

Step 4: Test in ADAS-Cog responder comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

Safety Analyses

The safety analysis population will include all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment actually received.

The following safety outcome measures will be summarized using descriptive statistics:

- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events

  Adverse events will be summarized by preferred term.
- Incidence of treatment discontinuations because of adverse events
- Mean changes in clinical laboratory tests from baseline over time and incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Incidence of anti-gantenerumab antibodies
- Physical and neurologic examination abnormalities

- Mean changes in vital signs assessment from baseline over time and incidence of abnormal vital sign measurements
- Changes in Columbia–Suicide Severity Rating Scale scores from baseline over time

Pharmacokinetic Analyses

Non-linear 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 PK model. The selection of parameters and the derivation of individual measures of exposure, such as $AUC_{0-\tau}$, C_{max}, and C_{trough}, will depend on the final PK model used for this analysis. All PK parameters will be presented by listings and descriptive summary statistics, including the arithmetic mean (for $AUC_{0-\tau}$, C_{max}, and C_{trough}), median, range, SD, and CV. Details of the mixed-effects modeling analysis will be described in the Modeling and Simulation Analysis Plan and results of this analysis will be reported separately. The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

Exploratory Analyses

An analysis will be performed to explore association of the treatment effect with patient genotypes to assess the influence of the APOE ε4 status and Fcγ receptor genotypes on the gantenerumab treatment effect, the primary efficacy variable, and selected safety parameters and summarized by each of the genotypes. Inferential statistics may be applied in case the difference is clinically relevant.

Determination of Sample Size

The purpose of this study was to test the treatment effect of gantenerumab relative to placebo. Point and interval estimates of the true treatment difference were to be presented.

A target sample size of 500 patients per arm was to be enrolled into the study. With this sample size, and based on the assumptions listed below, the study was estimated to have at least 80% power at a two-sided α level of 0.05 for testing the hypotheses of each of the co-primary efficacy endpoints using the MMRM analysis.

- Expected difference between treatment arms in the absolute change from baseline at Week 104 in ADAS-Cog13 of approximately 2.3 points, with a SD of 10.4
- Expected difference between treatment arms in the absolute change from baseline at Week 104 in ADCS-ADL of approximately 2.5 points, with a SD of 10.9
- Expected withdrawal rate (including censoring from the efficacy analysis owing to changes in medications) of approximately 30%

Subgroup Analyses

Since this is a global study, the effect of some demographic variables and baseline characteristic such as race and region on results of selected efficacy and safety variables will be summarized within subgroups using descriptive statistics (please see subgroups below). Additional exploratory analyses of efficacy results may be performed using an MMRM model, with the subgroup, a treatment-by-subgroup interaction term, and a subgroup-by-time interaction terms included along with the independent effects described above. This exploratory subgroup analysis may be important in understanding the effect of these variables on efficacy and safety. 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 ε4 status
- Fcγ receptor genotype
- Region

Additional subgroup analyses may be performed with subgroups defined based on baseline levels of CSF t-tau, p-tau, t-tau to Aβ1–42 ratio, and p-tau to Aβ1–42 ratio.

Since Part 1 (i.e., the double-blind period) has been suspended and replaced by an OLE, the primary and key secondary efficacy analyses will not be performed. However, exploratory and descriptive analyses will be conducted at the end of the study.

Interim Analyses

An interim analysis for futility was originally scheduled when approximately 50% of patients had completed 104 weeks of the double-blind treatment period. If at the time of the interim analysis, the tests of the co-primary endpoints indicated that the predictive probability of success was $<10\%$, then the trial may be terminated for futility.

This interim analysis was to be conducted by an independent Data Coordinating Center and will be reviewed by the independent Data Monitoring Committee.

There is no interim analysis scheduled for the OLE. However, the Sponsor will review the data on an ongoing basis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog	Alzheimer's Disease Activity Scale–Cognitive
ADCS-ADL	Alzheimer's Disease Cooperative Study–Activities of Daily Living
ADL	activities of daily living
ADNI	Alzheimer's Disease Neuroimaging Initiative
ADRDA	Alzheimer's Disease and Related Disorders Association
APA	American Psychiatric Association
APOE	apolipoprotein E
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin depositions
AUC	area under the concentration–time curve
BGTS	Barkhof Grand Total Score
BOLD	blood oxygenation level–dependent
BP	blood pressure
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating–Global score
CDR-SB	Clinical Dementia Rating–Sum of Boxes
ChEI	cholinesterase inhibitor
CHMP	Committee for Medicinal Products for Human Use
CL	Clearance
C_{max}	maximum plasma concentration
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CV	coefficient of variation
DRB	data review board
DS	Dependence Scale
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Version 5
EC	Ethics Committee
EEA	European Economic Areas
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
Fcγ	Fc gamma
FDA	U.S. Food and Drug Administration

Abbreviation	Definition
FLAIR	fluid attenuated inversion recovery
fMRI	functional magnetic resonance imaging
GAS	Goal Attainment Scaling
GDS	Geriatric Deterioration Scale
HbA_{1c}	hemoglobin A_{1c}
HCLF	high concentration liquid formulation
HIPAA	U.S. Health Insurance Portability and Accountability Act
IADL	Instrumental Activities of Daily Living
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
iDMC	independent Data Monitoring Committee
IEC	Independent Ethics Committee
IMC	internal monitoring committee
IMP	investigational medicinal product
iMRI-C	independent MRI committee
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	intent to treat
IxRS	voice/web response system
IV	Intravenous
LAR	legally authorized representative
LPLV	last patient, last visit
MAD	multiple ascending dose
MMRM	mixed-effects model repeated measures
MMSE	Mini Mental State Examination
MRI	magnetic resonance imaging
NCD	neurocognitive disorder
NINCDS	National Institute of Neurological and Communicative Disorders and Stroke
NPI	Neuropsychiatric Inventory
OFV	objective function value
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic
PRO	patient-reported outcome
p-tau	phosphorylated tau
q4w	every 4 weeks
QoL	quality of life

Abbreviation	Definition
qRT-PCR	quantitative reverse transcription polymerase chain reaction
RCR	Roche Clinical Repository
rs-fMRI	resting state functional magnetic resonance imaging
RUD-Lite	Resource Utilization Dementia–Lite
SC	subcutaneous
SD	standard deviation
SUVr	standardized uptake value ratio
T	Tesla
T_{max}	time to peak concentration
t-tau	total tau
ULN	upper limit of normal
VPC	visual predictive check
ZCI-AD	Zarit Caregiver Interview for Alzheimer's Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

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

AD is clinically characterized by a progressive impairment in cognitive and executive abilities, which results in decreased function and gradual loss of independence (Mesterton et al. 2010). 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 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 for decades to come.

The main pharmacologic approach to treatment aimed at limiting cognitive and functional decline in AD is to increase synaptic levels of acetylcholine through use of cholinesterase inhibitors (ChEIs). Currently available ChEIs include donepezil (Aricept®), galantamine (Reminyl®/Razadyne®), rivastigmine (Exelon®), and tacrine (Cognex®). Accumulating data have demonstrated that current pharmacotherapy provides limited symptomatic benefit; ChEIs can provide an improvement in cognitive function for 6–18 months followed by deterioration along a parallel path (Neugroschl and Sano 2010), whereas memantine (Namenda®) provides only modest improvement in global measures of functioning both with and without a ChEI (Neugroschl and Sano 2010). These medications have no effect on the progressing neuropathology (Gauthier et al. 2006; Hsiung and Feldman 2008; Schneider et al. 2011) and do not significantly change the course of the illness (Neugroschl and Sano 2010).

Increasingly, drug discovery and development in AD are focused on disease-modifying treatments that target amyloid-beta (Aβ) peptide, tau-opathies, and other pathologic consequences of AD. Modifying the course of AD could lead to significant public health benefits. For example, an intervention that could delay the onset of AD by 2 years could potentially decrease the incidence in such a way that in 50 years there would be nearly 2 million fewer cases than are currently projected (Neugroschl and Sano 2010).

The amyloid hypothesis is currently the most influential concept in the pathogenesis of AD and a powerful driver of drug development (Kurz and Perneczky 2011). According to the amyloid hypothesis, accumulation of Aβ in the brain is the primary factor driving AD pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe et al. 2012). The rest of the disease process, including tau phosphorylation and formation of neurofibrillary tangles, results from an imbalance between production and clearance of Aβ (Selkoe 1991; Hardy and Selkoe 2002). This imbalance is caused by overproduction of Aβ and by impaired clearance of Aβ from the brain. In addition to defective clearance of Aβ as a result of normal aging (Kress et al. 2014), reduced clearance can be caused by increased aggregation, defective degradation, disturbed balance of transport across the blood–brain barrier, or inefficient peripheral removal of the peptide (Kurz and Perneczky 2011). Accumulating evidence has suggested that monoclonal anti-Aβ antibodies can bind to Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), thus potentially reducing deposition of Aβ aggregates, reducing neurodegeneration, and slowing progression of AD. Additional evidence comes from recent findings on aducanumab (Biogen Idec), a high affinity, fully human IgG1 monoclonal antibody that targets fibrillar and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Hang et al. 2015). Specifically, results from an interim analysis of the Phase Ib study of aducanumab (BIIB037; PRIME study) on a total of 166 patients (placebo [n=40], 1 mg/kg [n=31], 3 mg/kg [n=33], 6 mg/kg [n=30], and 10 mg/kg [n=32]) with prodromal or mild AD, showed a dose- and time-dependent reduction of amyloid plaque in the brain that was associated with a beneficial clinical effect (Sevigny et al. 2015).

1.2 DIAGNOSTIC AND STATISTICAL MANUAL OF MENTAL DISORDERS, VERSION 5: MAJOR NEUROCOGNITIVE DISORDER DUE TO ALZHEIMER'S DISEASE

The Diagnostic and Statistical Manual of Mental Disorders, Version 5 (DSM-5; American Psychiatric Association [APA] 2013) formalizes a two-step method of diagnosis; first, a diagnosis of cognitive impairment is made, and then the underlying etiology is determined (APA 2013).

The DSM-5 does not use the term "Alzheimer's disease" alone as a diagnosis. The DSM-5 also replaces the term "dementia" with the term "major or mild neurocognitive disorder" (NCD; APA 2013). As such, mild AD is now referred to as major NCD due to AD, mild severity (APA 2013). Patients diagnosed with major NCD due to AD, mild severity have impairments in one or more cognitive domains, with progressive, gradual declines in learning and memory, intact instrumental activities of daily living (IADL), and evidence of no other etiologies.

This protocol will refer to the clinical diagnosis of AD according to the DSM-5 (i.e., as NCD due to AD, mild severity), which is consistent with the National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and

Related Disorders Association (NINCDS/ADRDA) criteria for mild severity (McKhann et al. 1984) and thus the protocol will use mild AD throughout.

1.3 BACKGROUND ON GANTENERUMAB

Gantenerumab, or RO4909832, is a fully human anti-Aβ peptide antibody developed by in vitro maturation within a complete human immunoglobulin (Ig) γ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ demonstrated for both major types of Aβ—that is, Aβ1–40 and Aβ1–42. Gantenerumab has an approximate molecular weight of 150 kDa. In vitro, gantenerumab recognizes aggregated Aβ with high affinity (Kd, ~0.5 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans gantenerumab may prevent, inhibit, or reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is in clinical development for patients with *early (*prodromal to mild*)* AD, and is also being investigated in carriers of familial AD mutations (DIAN-TU; Bateman et al. 2017).

Gantenerumab has been investigated in 10 completed Phase I clinical studies: three single ascending dose studies in healthy volunteers and patients with mild to moderate AD (Studies BN18726, JP22474, and BP30042); two multiple ascending dose (MAD) studies of patients with mild to moderate AD (Studies NN19866 and JP22431); and four bioavailability studies in healthy subjects, one comparing the intravenous (IV) and subcutaneous (SC) formulations of gantenerumab (Study WP22461), two comparing lyophilized and high-concentration liquid formulations (HCLFs) of gantenerumab (Studies WP27951 and BP29113), and one comparing drug substance manufactured through the third and fourth generation (G3 and G4) processes (Study WP40052). A tolerability study that compared injection-site pain between faster and slower SC administration of gantenerumab was also conducted (Study WP39322). Overall, a total of 543 subjects have received gantenerumab in the Phase I studies: 406 healthy volunteers and 101 patients with mild to moderate AD.

Gantenerumab is being investigated in four ongoing studies: a Phase III study investigating the effect of gantenerumab SC on cognition and function in patients with prodromal AD (Study WN25203), which has been converted to an open-label extension (OLE) study, a Phase II/III study (Dominantly-Inherited Alzheimer's Network Trials Unit [DIAN-TU-001]), and two pivotal Phase III studies (WN29922 and WN39658) investigating the effect of gantenerumab in prodromal to mild AD.

Clinical data supporting the use of gantenerumab in patients with AD came initially from the analysis of the NN19866-positron emission tomography (PET) study. In this randomized, double-blind, placebo-controlled study of mild to moderate AD, a small cohort of patients underwent PET with use of the Pittsburgh compound (^{11}C-PiB) as tracer to measure brain amyloid load after receiving 6 monthly doses of gantenerumab

IV (200 or 60 mg) or placebo. At 6 months, a significant decrease (approximately 20% relative change) in amyloid standardized uptake value ratio (SUVr) was seen in the 200-mg gantenerumab group relative to the 60-mg gantenerumab and placebo groups. These results, although representing a small sample, showed that gantenerumab is capable of exhibiting a biologic effect by decreasing brain amyloid load in a dose-dependent manner (Ostrowitzki et al. 2012). Safety findings from Study NN19866 showed that amyloid-related imaging abnormalities (ARIAs) were dose- and apolipoprotein E (APOE) ε4-dependent, with only the highest dose (200 mg IV every 4 weeks [q4w]) associated with amyloid-related imaging abnormality–edema/effusion (ARIA-E) findings. These data were used for initial dosing decisions (105 and 225 mg SC q4w), including APOE ε4-based dosing for Study WN25203.

In Study WN25203, while the doses under study were found not to have an effect on the primary endpoint, the Clinical Dementia Rating-Sum of Boxes (CDR-SB) at Week 104 compared to placebo, post-hoc clinical, and primary biomarker analyses revealed dose-dependent effects on PET SUVr, as well as drug concentration-dependent efficacy findings (see Section 1.4.1), indicative of the biological activity of gantenerumab seen in Study NN19866. Details of these findings are provided in subsequent sections of this document. See the Gantenerumab Investigator's Brochure (IB) for details on nonclinical and clinical studies.

1.3.1 Clinical Pharmacokinetics

The pharmacokinetic (PK) behavior of gantenerumab has been typical of an IgG. In general, peak plasma levels are reached within 1 to 6 hours following a 1-hour infusion, and concentrations decline thereafter in a biphasic manner with an apparent terminal half-life in the order of 24 days. Plasma exposure (maximum concentration [C_{max}] and area under the concentration time–curve [AUC]) is approximately in proportion to the dose over the range tested, although variability is moderately high (coefficient of variation [CV]: 11%–38% on repeated administration). Both systemic clearance (CL) and volume of distribution are low (CL: 7–29 mL/hr; volume at steady state: 3.5–24 L after multiple doses). Penetration into the CNS appears to be limited, and the cerebrospinal fluid (CSF) to plasma ratio is dose independent (approximately 0.1%–0.3%).

Absorption of gantenerumab is relatively slow after SC injection, with plasma concentrations reaching maximum levels generally 4–7 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. Two SC dose levels (75 mg and 150 mg) were investigated in an absolute bioavailability study (WP22461), and a higher range of dose levels (up to 1500 mg) were explored in a single-ascending dose study (BP30042). Bioavailability following SC administration was estimated to be between 55% and 67% (Study WP22461). A population PK model, built on available Phase I and

Phase III PK information, suggests a linear dose-proportional relationship over the dose range tested.

The metabolic and excretion pathways of gantenerumab have not been studied given that the antibody is expected to be metabolized in a similar way to endogenous IgG—that is cleavage to amino acids, which are renally excreted or re-utilized.

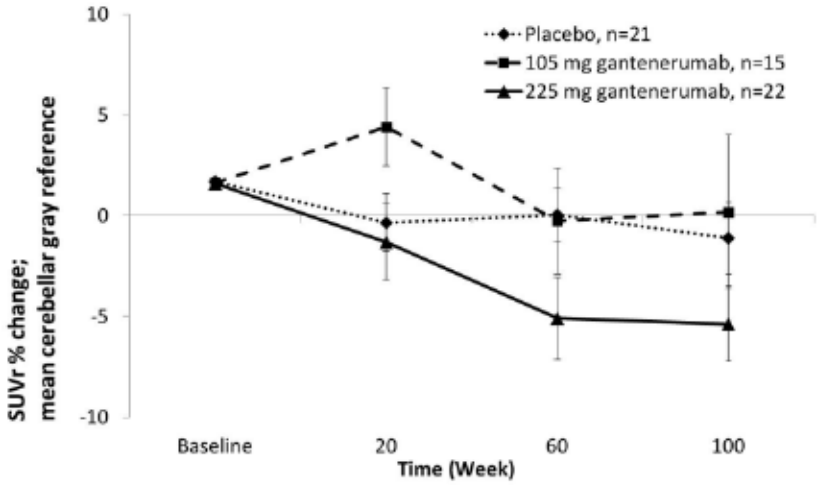
No drug–drug interaction studies have been conducted with gantenerumab; gantenerumab is not expected to interact with other drugs because the clearance pathways of IgG are distinct from those of small molecules. Gantenerumab is neither a cytokine nor a cytokine modulator, and no overt changes in immunomodulatory markers that might induce changes in cytochrome P450s were apparent in the CSF during the IV MAD study (NN19866). Clinical experience with concomitant use of AChEIs and memantine has been limited to the early single ascending dose (BN18726) and MAD (NN19866) studies, in which no apparent drug interactions were reported. The influence of concomitant medication on the pharmacokinetics of gantenerumab will be explored in a population PK assessment, which is included in this study (WN28745).

1.3.2 Pharmacodynamics

Study NN19866 included a PET substudy with scans performed at baseline and after 6 months of treatment. At approximately 6 months, a mean percentage SUVr decrease of –9.42 (median, –6.85) from baseline in the composite region was observed in the 200-mg gantenerumab group relative to an increase of 2.11 (median, 2.20) in the 60-mg gantenerumab group and an increase of 10.99 (median, 10.92) in the placebo group, which is in the expected range for this population (Lopresti et al. 2005; Ostrowitzki et al. 2012).

Study WN25203 also included a PET substudy that showed a dose-dependent reduction in Aβ SUVr, consistent with Study NN19866. Specifically, the mean percent changes from baseline in PET SUVr remained approximately the same in the placebo and 105-mg gantenerumab groups but decreased by approximately 5% in the 225-mg gantenerumab group over 2 years (see Figure 1).

Figure 1 Mean Percent Changes from Baseline in Composite Amyloid PET SUVr (Study WN25203, ITT Population)



ITT = intent to treat; PET = positron emission tomography; SE = standard error; SUVr = standardized uptake value ratio.
Mean ± SE.

1.3.3 Safety

Nonclinical characterization of gantenerumab did not show *any* relevant safety findings. To date, ARIA-E and amyloid-related imaging abnormality–hemosiderin depositions (ARIA-H) and injection-site reactions are *identified risks* for gantenerumab. No clinically relevant changes have been observed in laboratory parameters, physical and neurologic examinations, vital signs, or ECG parameters.

In Study NN19866, two serious adverse reactions, a cerebral microbleed and left bundle branch block, in 2 patients who had received 200 mg of gantenerumab were reported by the investigator to be related to study drug (for additional details, see the Gantenerumab IB). Neither event was considered by the Sponsor to be related to study drug following medical assessment of the event. With respect to standard safety measures, all doses were well tolerated (adverse events, laboratory tests, ECGs, and physical and neurologic examinations). ARIAs were observed at a dose of 200-mg IV in carriers of APOE ε4 allele and seemed more prominent in patients who were homozygous for APOE ε4. No ARIAs were observed at a dose of 60 mg IV in any genotype. With the exception of 1 patient homozygous for APOE ε4, ARIA findings remained clinically asymptomatic, and ARIA-E resolved spontaneously after treatment was stopped. No patients required treatment for ARIA. Monitoring for antibodies against gantenerumab did not reveal a signal of immunogenicity in the MAD Study NN19866.

Safety in Study WN25203, Double-Blind Treatment Phase

Study WN25203, a Phase III study investigating the effect of gantenerumab SC on cognition and function in prodromal AD, was unblinded following a pre-planned futility analysis. A total of 799 subjects were randomized (797 subjects treated) and received placebo (n = 266), 105 mg (n = 271), or 225 mg (n = 260) of gantenerumab SC q4w. Withdrawal for adverse events (including withdrawals due to protocol measures for management of magnetic resonance imaging [MRI] findings) was 5.3%, 8.5%, and 9.6% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively. Across the groups, the rates of serious adverse events were similar. No clinically relevant changes were observed in laboratory parameters, physical and neurologic examinations, vital signs, or ECG parameters. Overall, no new safety signals were identified; ARIA and injection site reactions remain the main clinical safety findings for gantenerumab.

ARIA events were manageable and were time-, dose-, and APOE ε4 status-dependent. Incidences of ARIA-E by treatment arm were 2 (0.8%) in placebo, 18 (6.6%) in the 105-mg gantenerumab, and 32 (12.3%) in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 29 (10.9%) in placebo and 52 (19.2%) and 34 (13.1%) in the 105 and 225 mg gantenerumab treatment arms, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.4% and 7.5%as compared to 0.9% and 0.5% between 9 and 12 months of treatment, in the 105- and 225-mg gantenerumab groups, respectively) and decreased substantially after the first year of treatment. Significantly, ARIA-E did not recur in subjects who restarted treatment at half of the original dose. Most ARIA events were asymptomatic (~90%), non-serious, of mild severity, had an MRI Barkhof Grand Total score (BGTS) median score of 3, with only 10% of ARIA-E scoring >10, and did not lead to more serious consequences. With respect to APOE ε4 status, WN25203 data are consistent with other anti-fibrillar Aβ data showing an increased rate of ARIA incidence for APOE ε4 carriers versus non-carriers (Salloway et al. 2014; Sperling et al. 2012b).

The overall incidence of injection site reactions 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, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively.

In Study WN25203, gantenerumab was safe and well tolerated, with an overall adverse event profile consistent with previous studies and expected findings in an elderly population.

Please refer to the Gantenerumab IB for *more detailed safety data from gantenerumab clinical studies.*

1.4 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

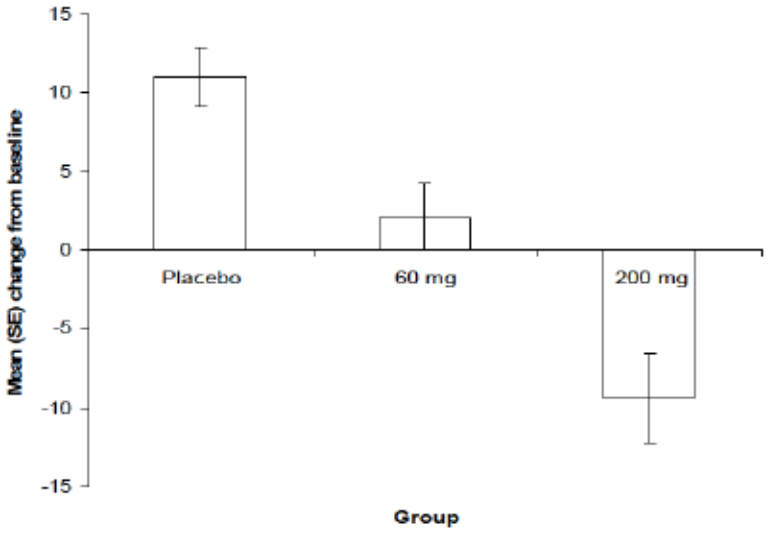
1.4.1 Study Rationale

1.4.1.1 Rationale for Part 1

As described in Section 1.3.2, data supporting the use of gantenerumab in patients with AD come from Studies NN19866 and WN25203, demonstrating its biologic effect in the brain.

In Study NN19866, brain amyloid was decreased in a dose-dependent manner in patients with mild to moderate AD who received doses of gantenerumab IV (200 mg or 60 mg) q4w compared with placebo (Ostrowitzki et al. 2012; Figure 2). These results showed that the mean percent change from baseline in SUVr (mean cerebellum reference) increased by 11% in the placebo group and by 2% in the 60-mg gantenerumab IV cohort, but decreased by 9% in the 200-mg gantenerumab IV cohort.

Figure 2 Amyloid PET Percent Change from Baseline: Composite Cortical Region at 6 Months (Study NN19866, ITT Population)



ITT = intent to treat; PET = positron emission tomography.

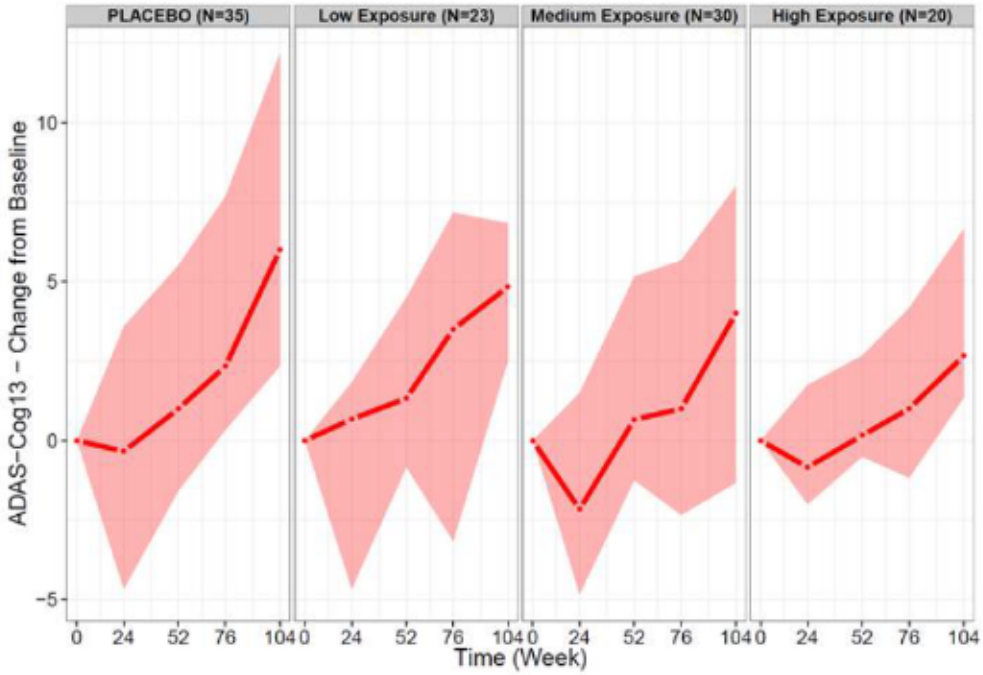
Based on the results from Study NN19866, a study in patients with prodromal AD was initiated (Study WN25203). Study WN25203 is a Phase III, adequate, and well-controlled, randomized, double-blind, placebo-controlled study, which enrolled 799 patients. The primary endpoint is the change from baseline in the CDR-SB at 2 years.

The primary purpose of Study WN28745 was to establish the efficacy and safety of gantenerumab as a disease-modifying treatment in patients with mild AD who may or may not be treated concurrently with approved treatments for AD.

1.4.1.2 Rationale for Part 2: Open-Label Extension

While the results of the pre-planned futility analysis of Study WN25203 showed no effect on the primary endpoint, a post-hoc analysis of patients predicted to be "fast progressors" (Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the Alzheimer's Disease Activity Scale–Cognitive (ADAS-Cog)-13, Mini Mental State Examination (MMSE), and CANTAB results. Figure 3 displays the results of placebo and gantenerumab concentration (three concentration groups) on ADAS-Cog-13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

Figure 3 Median Changes in ADAS-Cog Treatment Response by Plasma Concentration (Study WN25203, 2-Year Completing Fast Progressors)



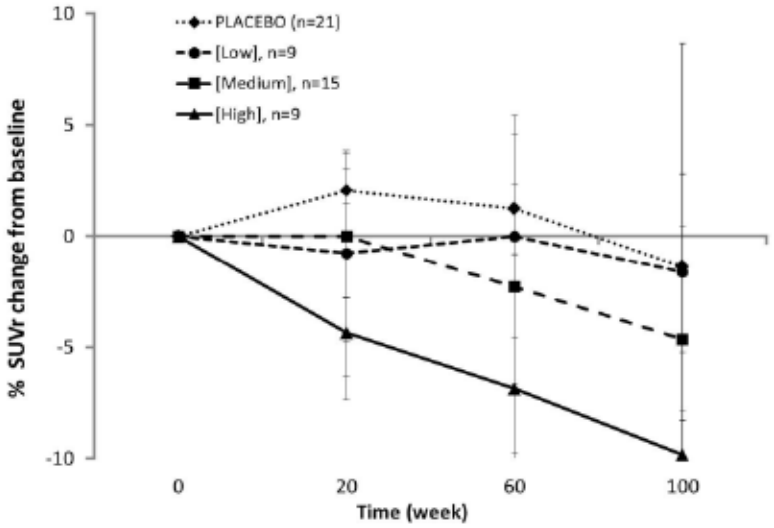
Dark red = median; red shaded = 50% observations.
Low = 1.48-5 µg/mL; Medium = 5–10 µg/mL; High = 10–26.68 µg/mL.

Furthermore, Study WN25203 contained a PET substudy with florbetapir F 18 (n = 114), which confirmed the reduction in brain amyloid by gantenerumab in a larger, less impaired patient sample than in Study NN19866. Dose- and time-dependent SUVr reductions were observed with 225-mg gantenerumab compared to placebo using the composite cortical SUVr and reference region of mean cerebellar grey. Week 100 results showed mean percent change from baseline in SUVr was −1.11, 0.19, and −5.37 in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 1). Results in a small number of patients on 225 mg gantenerumab over 3 years (n = 8; Week 156) suggested that the effect on SUVr reduction is continuous over

time because SUVr reductions with 225-mg gantenerumab compared to placebo increased with long-term exposure duration.

Study WN25203 concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration and SUVr reduction with greater average concentrations producing greater amyloid clearance. As seen in Figure 4, small changes in SUVr were present in the placebo and 1.9–5 µg/mL gantenerumab groups, while higher concentration groups (5–10 µg/mL gantenerumab and 10–20.72 µg/mL gantenerumab) displayed SUVr reductions of up to 5% and 10%, respectively. These analyses indicate that higher doses may produce greater Aβ clearance that may translate into greater clinical effect.

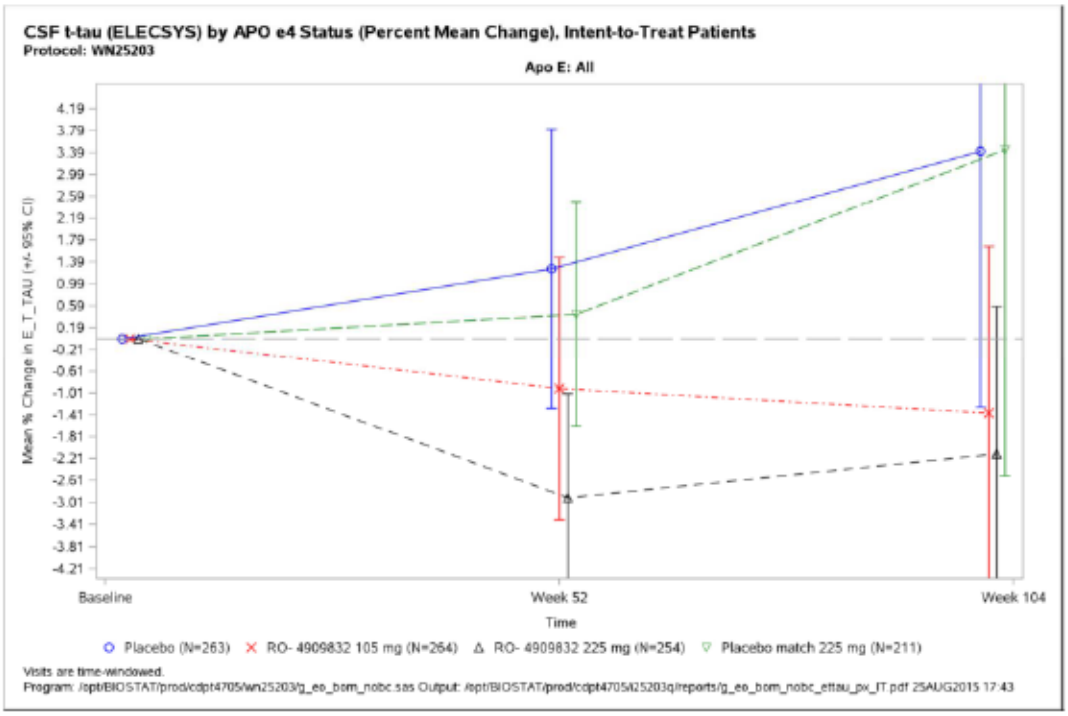
Figure 4 Median Changes in Concentration-Dependent PET SUVr Changes over Time, Cerebellum Grey Reference (Study WN25203, PET Substudy)



Median change ± 50% observation; PET = positron emission tomography; SUVr = standardized uptake value ratio.
Low = 1.9–5 µg/mL, Medium = 5–10 µg/mL, High = 10–20.7 µg/mL average plasma concentration.

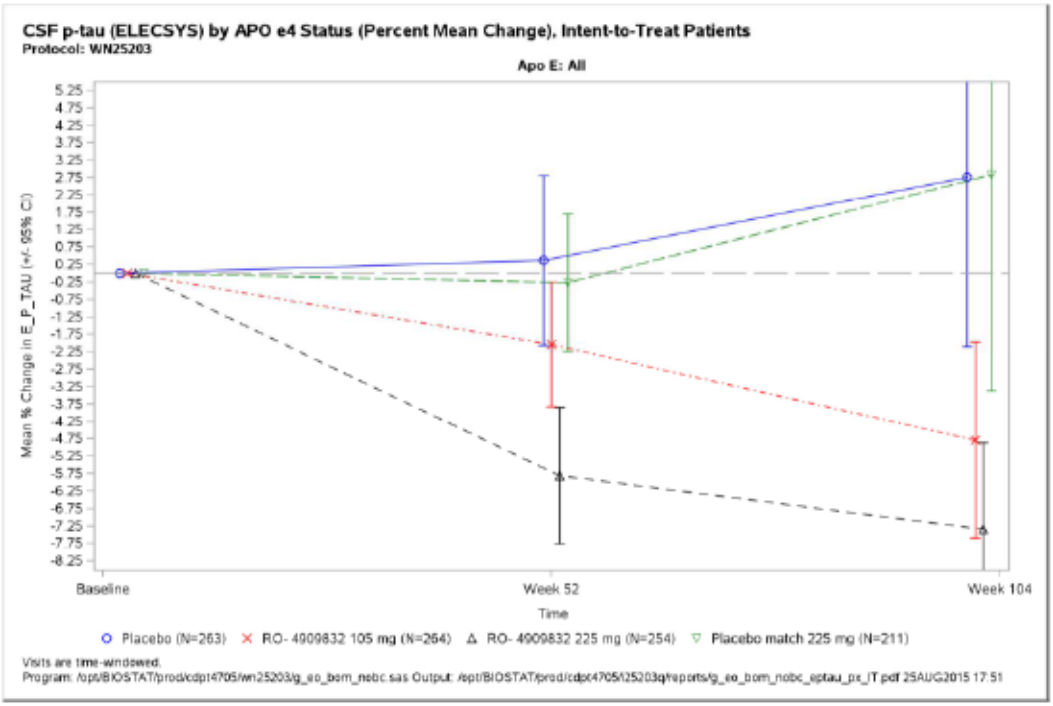
Finally, Study WN25203 CSF analyses showed dose-dependent reductions in both CSF tau species (total tau and phosphorylated tau) on gantenerumab compared with placebo with 225-mg gantenerumab q4w reducing tau species by approximately 10% at 2 years (p-tau $p < 0.01$; total tau $p = 0.09$) (see Figure 5 and Figure 6). No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab involving fibrillar over monomeric Aβ.

Figure 5 Mean Percent Changes from Baseline in CSF Total Tau by Treatment Group over 2 Years (Study WN25203, ITT Population)



CSF = cerebral spinal fluid; ITT = intent to treat.
Mean ± standard error.

Figure 6 Mean Percent Change from Baseline in CSF Phosphorylated Tau by Treatment Group over 2 Years



CSF = cerebral spinal fluid; ITT = intent to treat.
Mean ± 95%CI.

Overall, the findings in Studies NN19866 and WN25203 indicate the presence of clinical and biological activities of gantenerumab on major pathophysiological processes of AD. In addition, results from Study WN25203 suggested that higher doses may be required to reliably produce clinically significant results. This rationale receives further support from recent data with a similar mAb targeting fibrillar Aβ, aducanumab.

Aducanumab (Biogen Idec) and gantenerumab are very similar in that they both have affinity to the N-terminal conformational epitopes of Ab, target fibrillar and oligomeric forms of Aβ, and have a human IgG1 backbone enabling activation of microglia for immune-mediated clearance of amyloid plaques (Hang et al. 2015; Sevigny et al. 2015). Both compounds show a dose-dependent impact on SUVr reductions, with the changes reported in Study WN25203 appearing very similar to the results with 1 mg/kg aducanumab. Importantly, the 10 mg/kg dose of aducanumab was associated with significant clinical improvement. This dose would be equivalent to the higher gantenerumab target dose to be tested (Section 1.4.7). Modeling of the safety and efficacy outcomes of gantenerumab at higher doses is made possible by the strong similarity of the PK-PD activity of gantenerumab and aducanumab and publicly available aducanumab data; details of the modeling results are in Section 1.4.7.

Results from Study WN25203 indicate that the likelihood of the 225-mg dose of gantenerumab to achieve a clinical effect is very low. Along with data from the PRIME study (aducanumab), these findings indicate that higher doses are required to achieve clinical effect consistent with the biological activity represented by the amyloid and tau biomarker findings in Study WN25203. The purpose of Study WN28745 was to establish the efficacy and safety of gantenerumab as a disease-modifying treatment in patients with mild AD at 105- and 225-mg doses. Given that these doses are now considered subtherapeutic, the double-blind period of the study (considered as Part 1) was suspended and replaced with an OLE (Part 2) with increased dosing and a revised up-titration schedule. Therefore, the purpose of the OLE is to generate safety information on the higher doses and up-titration schedule while providing patients the opportunity to continue participating in an anti-amyloid treatment.

1.4.2 Rationale for Additional Years of OLE

As of 23 October 2017, a total of 383 patients have been enrolled into 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 2 years. Given that the safety profile of gantenerumab in the OLE studies remains similar compared with previous studies, the duration of the OLE will be increased until the end of 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.

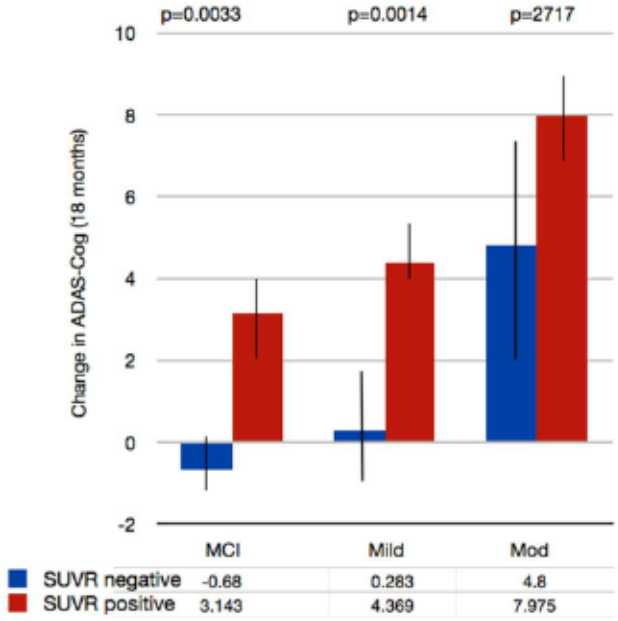
1.4.3 Rationale for Study Population

Because the accumulation of Aβ brain amyloid begins well before the onset of AD dementia, it is reasonable to postulate that the benefit of anti-amyloid therapy may be greater if initiated at an early stage of disease. This hypothesis is supported by the Phase III data from solanezumab in mild to moderate AD, where treatment effects were observed in patients with mild but not moderate AD.

An early intervention strategy is dependent on the ability to accurately identify patients with underlying AD pathology. The use of biomarkers in the patient population with mild AD is of importance because there is accumulating evidence that a significant number of patients in AD clinical trials may not have underlying amyloid pathology and thus may not be suitable for treatment with an anti-amyloid agent. Both solanezumab and bapineuzumab programs reported that approximately 20% overall of their respective mild to moderate clinical trial populations did not have amyloid pathology as measured on PET (Doody 2012; Sperling et al. 2012b). This proportion was approximately 36% in APOE ε4 non-carriers. Furthermore, data reported by Avid Radiopharmaceuticals at the American Academy of Neurology meeting in 2013 demonstrated that cognitive decline, as measured by the ADAS-Cog over 18 months, was observed only in patients with prodromal or mild AD who had evidence for increased brain amyloid on PET

(Siderowf et al. 2013; see Figure 7); there was no effect of brain amyloid on cognitive decline in moderate AD.

Figure 7 Amyloid-Dependent Progression in MCI and Mild AD



AD = Alzheimer's disease; ADAS-Cog = Alzheimer's Disease Activity Scale–Cognition; SUVr = standardized uptake value ratio; MCI = mild cognitive impairment.
Source: Siderowf et al. 2013.

Consistent with this concept, this study enrolled patients who met the criteria for diagnosis of probable mild Alzheimer's dementia based on NINCDS/ADRDA criteria or probable major NCD–mild severity based on the DSM-5 criteria; biomarker evidence for β-amyloid deposition as demonstrated by decreased CSF Aβ1–42 levels (i.e., ≤700 pg/mL measured on the Roche Elecsys® assay); MMSE score at screening between 20 and 26, inclusive; Clinical Dementia Rating Scale–Global Score (CDR-GS) 0.5 or 1.0 at screening; and screening Geriatric Depression Scale (GDS)-15 score <6.

The CSF Aβ1–42 threshold is based on extensive literature derived from multicenter studies in the United States and Europe and represents the natural cutoff between AD and non-AD biomarker profiles observed in AD populations. The DSM-5 criteria for NCD due to AD, mild severity are considered consistent with the NINCDS/ADRDA criteria for mild AD (McKhann et al. 1984); this protocol will use mild AD throughout.

The patient selection approach is consistent with the National Institute on Aging/Alzheimer's Association's updated diagnostic research criteria for AD dementia as well as with the Qualification Opinion from the European Medicines Agency's (EMA)

Committee for Medicinal Products for Human Use (CHMP) on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (EMA 2012). The use of CSF biomarkers for trial enrichment is also supported by the U.S. Food and Drug Administration's (FDA's) draft guidance for early AD (FDA 2013). Although the guidance refers to the early stage of AD in which individuals present with mild cognitive impairment, CSF biomarkers are expected to also add value to patient selection in mild AD trials (FDA 2013).

In addition, a subset of consenting patients are participating in a substudy of PET brain, or PET brain and heart imaging using a florbetapir F 18 injection (Avid Radiopharmaceuticals; Philadelphia, PA). Details of these substudies are described in two separate protocols (WN28745-PET and WN28745-Cardiac PET).

1.4.4 Rationale for Pharmacokinetic Sampling

A population PK analysis will be performed to allow the determination of the pharmacokinetics of gantenerumab in the target population with use of a sparse PK sampling strategy. This approach will investigate the sources of variability in the pharmacokinetics of gantenerumab in the target population that may be explained by patient characteristics, such as age, sex, and body weight. Furthermore, the influence of background medication on the pharmacokinetics of gantenerumab will be explored. If appropriate, concentration–effect relationships may be assessed and modeled for pharmacodynamic (PD), efficacy, or safety measures.

If ARIA findings occur, additional PK samples will be obtained to explore the underlying relationship between ARIA and PK parameters.

1.4.5 Clinical Relevance and Risk-Mitigation Measures for ARIA Findings

Clinical experience with gantenerumab has revealed that ARIA-E events were dose-, time-, and ApoE4-dependent, and well-managed through MRI monitoring and dose intervention algorithms. The vast majority of patients with ARIA-E reported no symptoms, and the ARIA-E resolved spontaneously when study drug was withheld. 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.

ARIA-H events were dose- and ApoE4-dependent, and all ARIA-H events (in patients without ARIA-E) were asymptomatic. ARIA-H is managed through MRI monitoring and dose intervention algorithms.

The mechanism underlying the development of ARIA-E (vasogenic edema) during anti-amyloid treatment is not known. It has been hypothesized that because amyloid is removed it may lead to transiently increased cerebrovascular amyloid (Weller et al. 2009). Targeting removal of Aβ from both parenchyma and the cerebral vasculature, vessels with preexisting amyloid vascular pathology might become transiently more susceptible to leakage of vascular contents. This pathology results in ARIA-E if the leakage is of proteinaceous fluid, and ARIA-H if the leakage is of heme-based blood products (Sperling et al. 2012b).

In Part 1 of this study, imaging-related criteria were used to exclude patients with cerebral vascular disease, as well as ARIA-related lesions. MRI monitoring was conducted during the study at regular intervals (see Schedule of Assessments for the up-titration and MRI schedules, Appendix 1). If ARIA findings occurred, more intense MRI monitoring, dose adjustments (including temporary dose holding), and permanent discontinuation were implemented according to an ARIA-related dose-adjustment plan, described in Section 5.1.4.1. Safety findings (including unblinded cases and reports) were reviewed on a regular basis (e.g., quarterly) by the independent Data Monitoring Committee (iDMC).

In Part 2, MRI monitoring will be conducted at regular intervals (see OLE Schedule of Assessment for up-titration and MRI schedules, Appendix 2). In addition, more intense MRI monitoring, dose adjustments (including temporary dose holding), and permanent discontinuation will be implemented following ARIA findings as described in Section 5.1.4.2. ARIA findings will be monitored on an ongoing basis by the Sponsor (internal monitoring committee [IMC]) and an independent MRI committee (iMRI-C). The iDMC will also be reviewing relevant safety findings on a regular basis until the majority of patients have reached the target dose (expected March 2018). 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. Adverse events known to be associated with gantenerumab include injection-site reactions and ARIA. Most injection-site reactions have been mild in intensity and have not required treatment. Incidence of ARIA findings has been as expected with the majority of events being non-symptomatic and well controlled by protocol defined management rules. Given that enrollment into the OLE is closed, most patients will have reached the target dose by March 2018. Once the majority of patients have reached the target dose, the iMRI-C and the IMC will continue to review safety findings on a regular basis. Any new relevant findings identified either through the IMC or iMRI-C may be submitted to the Phase III studies (WN29922 and WN39658) iDMC.

1.4.6 Risk to Patients without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of CSF $A\beta_{42}$, only patients with AD pathology were likely to be enrolled in Part 1. In patients without underlying amyloid pathology, gantenerumab is not expected to have any

biologic effect because it is an engineered, fully human monoclonal antibody with extremely high selectivity and specificity for aggregated Aβ. Therefore, it is unlikely that patients who do not have amyloid pathology would benefit from gantenerumab.
In addition, only patients who are enrolled in the double-blind treatment period at the time of this protocol amendment will be eligible to enroll in the OLE.

1.4.7 Rationale for the Dosing Strategy

1.4.7.1 Rationale for the Dosing Strategy in Part 1

In this study, all patients regardless of APOE ε4 status were eligible to receive a dose of 225 mg SC gantenerumab q4w (or placebo). All patients were initially treated with 105 mg SC gantenerumab (or placebo) for the first 24 weeks, following MRI confirmation supporting the lack of ARIA-E and no more than one new ARIA-H on MRI after the Week 24 dose, all patients then had the dose increased to 225 mg SC (or placebo) starting with the Week 28 dose (see Section 5.1.4). This dose-titration strategy of 105 mg SC for the first 24 weeks of dosing and 225 mg SC thereafter for all patients was supported by the Phase I MAD Study NN19866, the blinded to-date safety profile in Study WN25203, and a comprehensive strategy for ARIA monitoring (as well as the appropriate actions to take if these events are detected), as included in this protocol.

SC dosing in Study WN25203 in patients with prodromal AD was stratified, depending on the patient's APOE ε4 status. The relative bioavailability for the SC formulation is approximately 60% of that for the IV formulation. Accordingly, the doses in Study WN25203 were 105 mg SC (comparable in exposure to the MAD dose of 60 mg IV that was not associated with ARIAs and prevented amyloid accumulation), and 225 mg SC, which was associated with exposure approximately 60% of that for the 200-mg IV dose, reduced amyloid and for which reversible ARIA-Es were detected in the heterozygous APOE ε4 carriers. While the MAD Study NN19866 demonstrated a dose-dependent effect on amyloid removal, there was also a dose- and APOE ε4 genotype−related increased incidence of ARIAs. Study WN25203 has also been converted to an OLE study.

Clinical experience in Study WN25203 showed that ARIAs were manageable with inclusion/exclusion criteria, MRI monitoring, and dose change algorithms and did not appear to lead to significant adverse outcomes. Please refer to the current Investigator's Brochure for additional details.

Sperling et al. (2012b) suggest that because brain vascular amyloid is cleared with immunotherapy, the underlying impaired vasculature may be exposed, leading to a transient vulnerability period that may manifest with fluid or blood leakage into the parenchyma, thereby creating the MRI abnormalities (ARIA-E and ARIA-H, respectively). Thus, ARIA may represent a transient worsening of underlying cerebral amyloid angiopathy caused by a more rapid amyloid clearance process following the initiation of amyloid-removal therapy.

The up-titration strategy aimed to clear amyloid more slowly during the initial period when patients appear most prone to develop ARIAs. Thus, if a patient was treated with a low dose of gantenerumab and did not develop ARIA-E or more than one new microbleed after the first 24 weeks, the patient was eligible to titrate to the high dose, and it could be reasonably expected that the patient would continue to tolerate the high dose of gantenerumab for the duration of the study.

MRI monitoring for ARIA-related events at regularly scheduled intervals, as defined in the schedule of assessments (see Appendix 1), with higher frequency during the initial 12-month treatment period, ensured appropriate detection of all ARIAs (including asymptomatic events) and allowed clinically appropriate measures to be taken on a patient level (see Section 5.1.4). This also ensured close clinical monitoring for Apo ε4 homozygous patients during their exposure to the 225 mg dose.

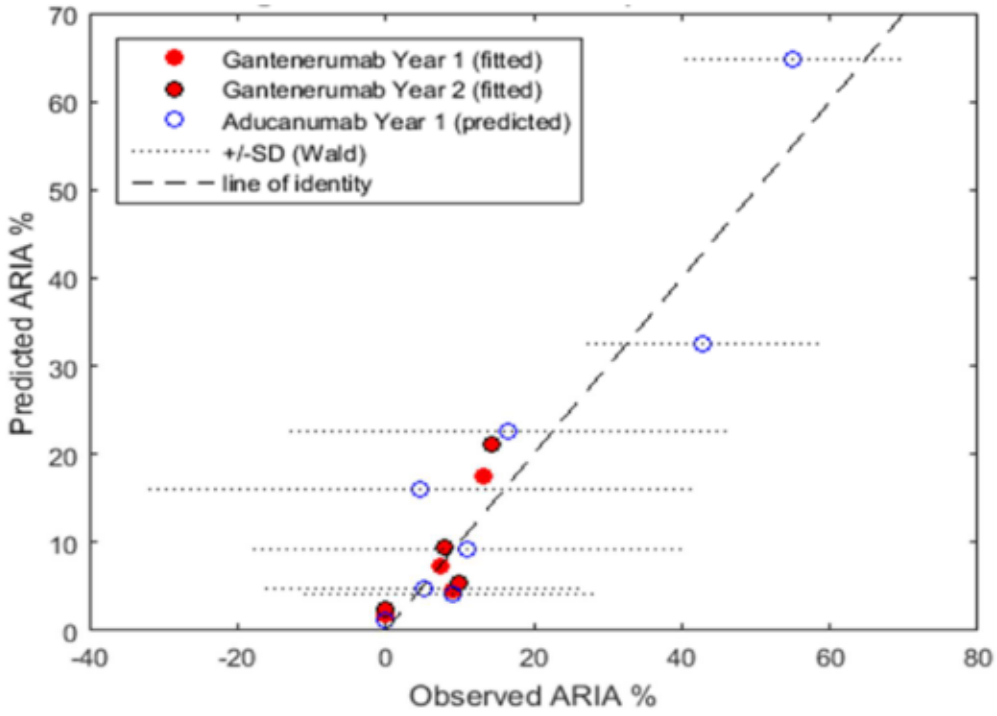
Given the ability to monitor for ARIA, coupled with the potentially limited clinical significance of these phenomena in many cases, this strategy aimed to optimize the safety profile of gantenerumab while maximizing the potential for amyloid removal in all patients, regardless of their APOE ε4 status.

1.4.7.2 Rationale for the Dosing Strategy in Part 2

Doses for Study WN25203 (105 and 225 mg SC q4w) were based on earlier findings from Study NN19866 that suggested approximately 20% mean reduction from baseline in amyloid SUVr over 2 years at the 225-mg dose relative to placebo. However, results from Study WN25203 indicated that the SUVr reductions were approximately 5% from baseline over 2 years. Therefore, to obtain efficacious levels of amyloid SUVr reduction, higher doses of gantenerumab will be required.

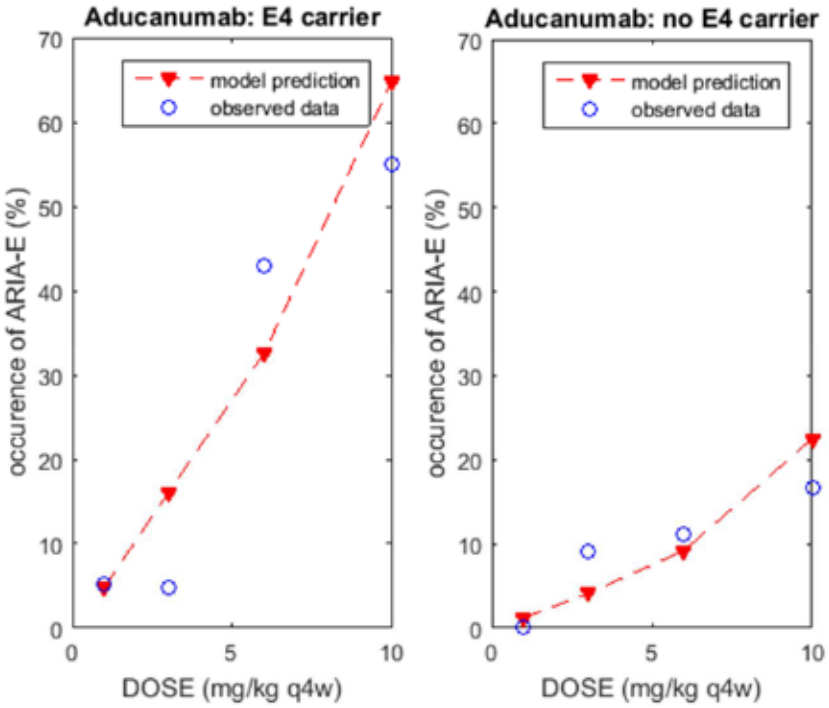
Given the absence of human exposure data on higher doses of gantenerumab and recognizing the PK-PD similarities of gantenerumab and aducanumab, a model was developed to predict both the safety and efficacy outcomes of higher gantenerumab doses. The safety model also provided the opportunity to test the hazard PK-PD model applied to gantenerumab on aducanumab IV using the bapineuzumab data. This model predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (Figure 8), including the ARIA rate differences across APOE ε4 allele groups (Figure 9).

Figure 8 ARIA-E Prediction for Aducanumab IV Using Bapineuzumab Hazard Model Adapted to Gantenerumab SC



ARIA-E = amyloid-related imaging abnormality–edema/effusion; ITT = intent to treat; IV = intravenous; SC = subcutaneous; SD = standard deviation.

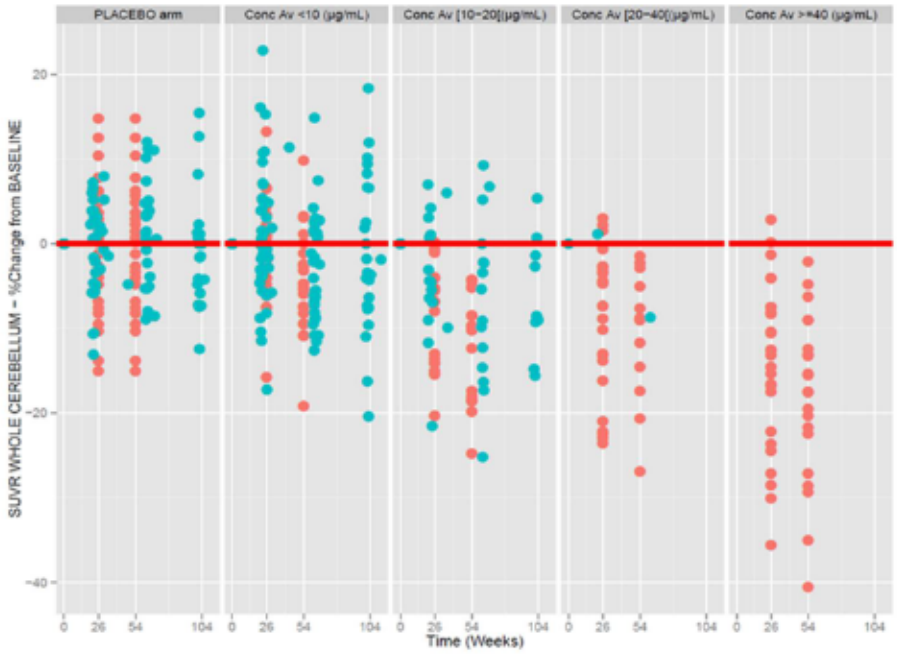
Figure 9 Model-Based Predictions of ARIA-E Occurrence for Aducanumab per APOE-E4 Carrier (Left)/Non-Carrier (Right) and per Dose for an Every 4 Weeks Dosing Regimen. Comparison to Observed Data in PRIME Study



APOE=apolipoprotein E; ARIA-E=amyloid-related imaging abnormality–edema/effusion; q4w=every 4 weeks.

From an efficacy perspective, comparison of the amyloid PET-time course of both compounds per range of serum concentration level first confirmed that both drugs share the same PK-PD relationship for amyloid PET reduction (Figure 10).

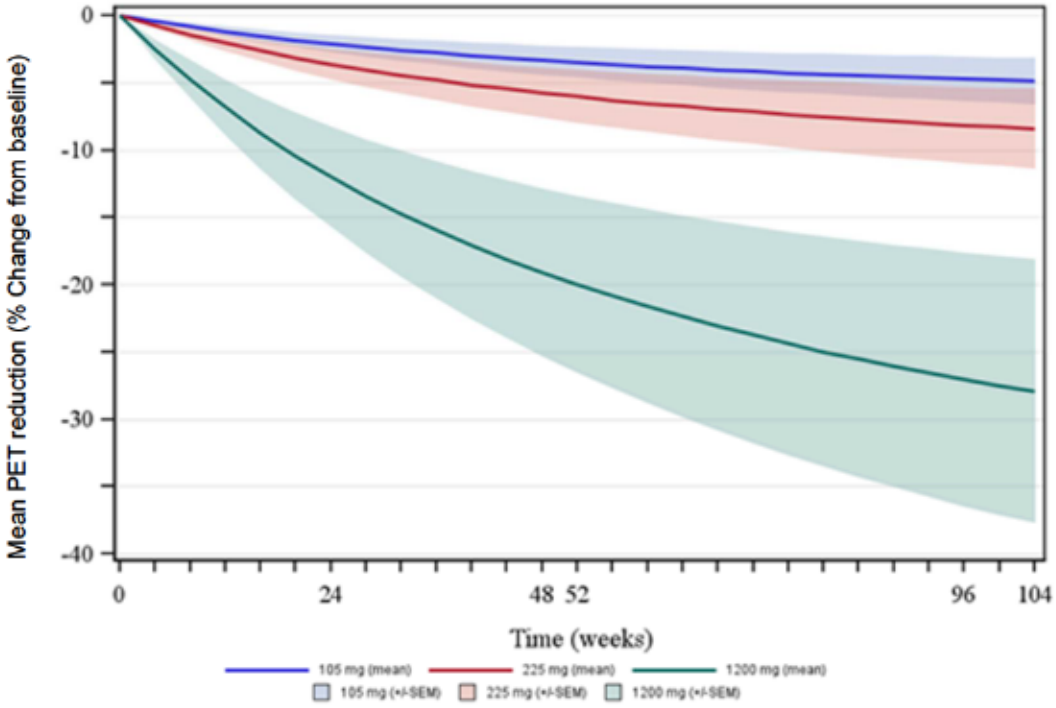
Figure 10 SUVr Percentage Change from Baseline Time Course per Category of Drug-Concentration and Drug Type



Gantenerumab Study WN25203 data in blue, Aducanumab PRIME data in red.
SUVr = standardized uptake value ratio.

In addition, the model indicated that higher doses of gantenerumab are needed to achieve a clinical response similar to aducanumab 10 mg/kg, where a clinical response (on both the MMSE and CDR) was present. This range was associated with a 15%–20% PET reduction from baseline at 1 year; the dose of gantenerumab predicted to achieve the same response is 1200 mg q4w (Figure 11).

Figure 11 Mean Predicted PET Reduction (±SEM), Illustrated for Doses 105, 225, and 1200 mg–q4w Dosing



PET = positron emission tomography; SEM = standard error of mean.

To minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, different titration schemas were modelled. A titration schedule predicted to produce clinically acceptable ARIA-E rates over 2 years regardless of APOE ε4 status was chosen. Generally, this schedule uses lower starting dose and longer titration duration for APOE ε4 carriers. This approach is expected to generate SUVr reductions associated with clinical benefit for both APOE ε4 carriers and non-carriers, respectively (see Table 1).

Table 1 Predicted Mean ARIA-E Occurrence (%) and PET Reduction (%) after 1 Year (Y1) and 2 Years (Y2) of Treatment in Part 2 for the Proposed Titration Schedules

Apoe ε4 status	Dose received in Part 1	Titration schemes[a]	Predicted mean ARIA-E occurrence (%)		Predicted mean PET reduction (%)	
			Y 1	Y 2	Y 1	Y 2
C	225(6)	450(2) 900(2) 1200(20)	25	27	19	27
NC	225(6)	600(2) 1200(22)	7	8	19	27
C	105(6)	225(2) 450(2) 900(2) 1200 (18)	15	18	16	26
NC	105(6)	300(2) 600(2) 1200(20)	4	5	17	26
C	0(6)	225(2) 450(2) 900(2) 1200 (18)	37	41	16	26
NC	0(6)	300(2) 600(2) 1200(20)	13	13	17	26

Note: Predictions given according to the APOE ε4 status (Carriers [C] or Non-Carriers [NC]) and according to the dose received in Part1 during the previous 6 months.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = positron emission tomography.

- Expressed as dose in mg (number of administrations).

Therefore, in the OLE, all participating patients, regardless of APOE ε4 status, will be eligible to receive the target dose of 1200 mg gantenerumab SC q4w, and the APOE ε4 status (0ε4 'non-carriers' and 1ε4/2ε4 'carriers') will define the titration rate with carriers having a more gradual up-titration schedule to decrease the risk of ARIA findings while optimizing treatment effect. The different up-titration schemes as per APOE status and previous treatment assignment (gantenerumab or placebo) will allow to safely examine a range of starting doses for patients previously on placebo including the 225 mg and 300 mg q4w for carriers and non-carriers. In addition, it will allow for patients previously on gantenerumab to achieve potentially therapeutic doses as quickly and safely as possible.

Please refer to Appendix 4 for additional information on modeling and simulation.

There will be a total of four titration schedules as follows:

1. Carrier patients previously on 225 mg gantenerumab
2. Non-carrier patients previously on 225 mg gantenerumab
3. Carrier patients previously on 105 mg gantenerumab or on placebo
4. Non-carrier patients previously on 105 mg gantenerumab or placebo

Patients who were on 225 mg gantenerumab will be up-titrated according to their APOE ε 4 status as follows: Carriers will be up-titrated to 450 mg for 2 months, followed by 900 mg for 2 months, and then 1200 mg for the duration of the OLE. Non-carriers will

be up-titrated to 600 mg for 2 months followed by 1200 mg for the duration of the OLE (see Table 2).

Similarly, patients who were on 105 mg gantenerumab or placebo will be up-titrated according to their APOE ε4 status as follows: Carriers will be initially treated with 225 mg for 2 months, then up-titrated every 2 months to 450 mg followed by 900 mg until they reach 1200 mg; non-carriers will initially be treated with 300 mg for 2 months then up-titrated to 600 mg for 2 months followed by 1200 mg for the duration of the OLE (see Table 2).

At every dose increase, MRI confirmation of no symptomatic ARIA-E, no ARIA-E with BGTS > 1, or no more than eight ARIA-H cumulatively as per Section 5.1.4 will be required. Patients who do not meet the criteria for up-titration will either remain on the same dose or may be temporarily discontinued from treatment until satisfactory resolution of MRI finding (see Section 5.1.4).

Table 2 Up-Titration Schedule for Open-Label Extension

Previous Treatment Assignment (APOE ε4 status)	OLE [a] Day 1	OLE Week 4	OLE Week 8	OLE Week 12	OLE Week 16	OLE Week 20	OLE Week ≥ 24
225 mg Gantenerumab (Carriers)	450	450	900	900	1200	1200	1200
225 mg Gantenerumab (Non-carriers)	600	600	1200	1200	1200	1200	1200
105 mg Gantenerumab or Placebo (Carriers)	225	225	450	450	900	900	1200
105 mg Gantenerumab or Placebo (Non-carriers)	300	300	600	600	1200	1200	1200

APOE = apolipoprotein E; ICF = informed consent form; OLE = Open-Label Extension.
Note: All numerical amounts presented above are in milligrams (mg).
[a] First open-label gantenerumab dose administered following signature of Part 2 ICF.

The APOE ε4 up-titration strategy with regular MRI monitoring prior to each dose increase aims to slowly clear amyloid during the initial period when patients appear most prone to develop ARIA. If a patient does not develop a symptomatic ARIA-E, an ARIA-E with BGTS > 1, or more than eight microbleeds cumulatively, the patient will be eligible to progress through the up-titration schedule to the target dose. Once a patient reaches

the target dose, it can be reasonably expected that the patient would continue to tolerate this dose for the duration of the study.

MRI monitoring for ARIA-related findings at regularly scheduled intervals (prior to each up-titration), as defined in the schedule of assessments (see Appendix 2), will ensure appropriate detection of ARIAs (including asymptomatic events) and allow clinically appropriate measures to be taken on a patient level (see Section 5.1.4). This also ensures close clinical monitoring for all patients during their up-titration and exposure to higher doses.

This dosing strategy aims to optimize the safety profile of gantenerumab while maximizing the potential for amyloid removal in all patients, regardless of their APOE ε4 status.

1.4.8 Overall Benefit–Risk Summation

Overall, the benefit–risk assessment of gantenerumab is based on the following:

- Gantenerumab has a proven effect on amyloid plaques and, thus, potential benefit in slowing the progression of AD.
- Findings from *Study* WN25203 and aducanumab PRIME studies provide additional support that anti-amyloid treatment may be associated with *a* beneficial clinical effect.
- *Results from the double-blind portions, as well as from the OLEs, of Studies WN25203 and WN28745 have shown that ARIA findings are mostly asymptomatic, non-serious, and mild in severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.4.*
- *No new safety signal has been identified in data from ongoing OLE studies with gantenerumab (manufactured through G3 process) at doses of up to 1200 mg administered every 4 weeks.*

The Sponsor concludes the benefit–risk profile of gantenerumab in the population with mild AD is favorable for higher doses of up to 1200 mg SC q4w. In addition, the Sponsor concludes that an OLE study will offer the added benefit of long-term safety characterization with respect to both the higher doses and the different titration regimen of gantenerumab.

2. OBJECTIVES

2.1 PART 1 OBJECTIVES

2.1.1 Efficacy Objectives

The primary efficacy objective of this study was to evaluate the efficacy of gantenerumab compared with placebo administered to patients by SC injection over 100 weeks as measured by the following co-primary endpoints (final outcome assessment 4 weeks after the final dose):

- Cognition, as measured by the ADAS-Cog (13-item)
- Function, as assessed by the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL)

The key secondary efficacy objectives for this study was to evaluate the benefits of gantenerumab versus placebo administered to patients by SC injection over 100 weeks on slowing clinical decline and disease progression by assessing the following key secondary endpoint domains:

- Time to clinically evident decline, as determined by:

  Confirmed decline of ≥ 2 points (at two consecutive visits) on the MMSE, and

  Loss of ≥ 1 points on one or more basic ADL, as measured on the ADCS-ADL or

  Loss of ≥ 2 points on one or more IADL, as measured on the ADCS-ADL
- Change from baseline at Week 104 in CDR-SB
- ADAS-Cog responder(see the Statistical Analysis Plan for more details)
- Disease pathology biomarkers:

  Effect of gantenerumab on CSF biomarkers reflecting AD pathology (i.e., Aβ1–42, total tau [t-tau] and phosphorylated tau [p-tau])

  Effect of gantenerumab on neurodegeneration, measured using structural (whole brain and regional brain atrophy) MRI before, during, and after treatment

The following additional secondary endpoints and their respective domains were to be evaluated:

- Global

  Effect on severity of dementia, assessed using the CDR-GS
- Cognition

  Effect on cognition, assessed using the MMSE

  Effect on cognition assessed with the ADAS-Cog13 using a responder analysis, for which response is defined as an increase of ≤ 4 points on the ADAS-Cog13 from baseline (i.e., worsening)

- Behavior

  Effect on behavioral and neuropsychological symptoms of AD, assessed using the NPI

Other AD symptoms and effects:

- Effect of gantenerumab on health-related quality of life (QoL), assessed using the Quality of Life–AD (QoL-AD) scale
- Effect of gantenerumab on patient-individualized goal achievement using the SymptomGuide™ Facilitated Goal Attainment Scaling (GAS; to be conducted at sites in English and French speaking countries only)
- Effect of gantenerumab on caregiver emotional well-being using the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale
- Effect of gantenerumab on the amount of assistance patients with dementia require in performing daily activities, using the Dependence Scale (DS) and Resource Utilization Dementia–Lite (RUD-Lite)

2.1.2 Safety Objectives

The safety objectives for this study were as follows:

- To evaluate the safety of gantenerumab compared with placebo in patients with mild AD, focusing on physical and neurologic examinations, vital signs, blood safety tests, ECGs, and adverse event monitoring
- To evaluate the safety of gantenerumab compared with placebo in patients with mild AD, focusing on adverse events as assessed on MRI:

  ARIA-E

  ARIA-H
- The development of anti-gantenerumab antibodies, referred to as anti-drug antibodies (ADAs) (also known as human anti–human antibodies)

  The development of ADAs will be assessed, and if detected, whether there is an association with the PK, PD, efficacy, and safety parameters following treatment with gantenerumab.

2.1.3 Pharmacodynamic Objectives

The PD objective of this study was to assess changes in amyloid load in the brain and heart over time using a florbetapir F 18 injection (Amyvid™), a PET radioligand selective to β-amyloid, in patients with mild AD (as determined by clinical criteria and Aβ CSF) who are treated with gantenerumab or placebo.

The PD objective will be evaluated in a subset of consenting patients (approximately 60 patients in the PET substudy assessing brain amyloid, 5 of whom also participated in the cardiac PET substudy). Details of the PET substudies are described in separate protocols (WN28745-PET and WN28745-Cardiac PET).

2.1.4 Pharmacokinetic Objectives

The PK objectives for this study were to explore the pharmacokinetics of gantenerumab in patients with mild AD and the influence of covariates on the PK behavior.

2.1.5 Exploratory Objectives

The exploratory objective of this study was to evaluate if the removal of Aβ by gantenerumab in the brains of patients with mild AD will modulate functional brain connectivity (i.e., increase brain functional connectivity using resting state functional magnetic resonance imaging [rs-fMRI]) compared with patients treated with placebo.

Exploratory biomarkers will be assessed in consenting patients.

The Roche Clinical Repository (RCR) is a centrally administered group of facilities for the long-term storage of human biologic specimens. Specimens for the RCR will be collected from patients who give specific consent to participate in this optional research. Specimens stored in the RCR will be used to:

- Study the association of biomarkers with efficacy and/or adverse events associated with the medicinal product
- Increase our knowledge and understanding of disease biology
- Study drug response, including drug effects and the processes of drug absorption and disposition
- Develop biomarker or diagnostic assays and establish the performance characteristics of these assays

For additional details about RCR sampling, please refer to Section 4.5.15, Samples for Roche Clinical Repository.

2.2 PART 2 OBJECTIVES

The main objective of the OLE is to evaluate the safety and tolerability of gantenerumab at higher doses focusing on physical and neurologic examinations, vital signs, blood safety tests, ECGs, and adverse event monitoring. All patients previously enrolled and ongoing in the study will be eligible to receive active gantenerumab and will be up-titrated gradually to the highest possible dose up to 1200 mg.

The secondary objectives will include the following:

- To evaluate the effect of higher doses of gantenerumab on imaging biomarkers (PET and MRI) on CSF biomarkers and on clinical outcome measures (cognition and function) over time
- To explore pharmacokinetics at the higher gantenerumab doses

3. STUDY DESIGN

3.1 DESCRIPTION OF STUDY

3.1.1 Overview of Study Design in Part 1

The study was a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of gantenerumab in patients with mild AD. Patients with mild AD were selected on the basis of clinical diagnosis of probable mild AD according to the NINCDS/ADRDA criteria or probable NCD due to AD, mild severity using the DSM-5 criteria, and biomarker evidence for increased amyloid burden (McKhann et al. 1984).

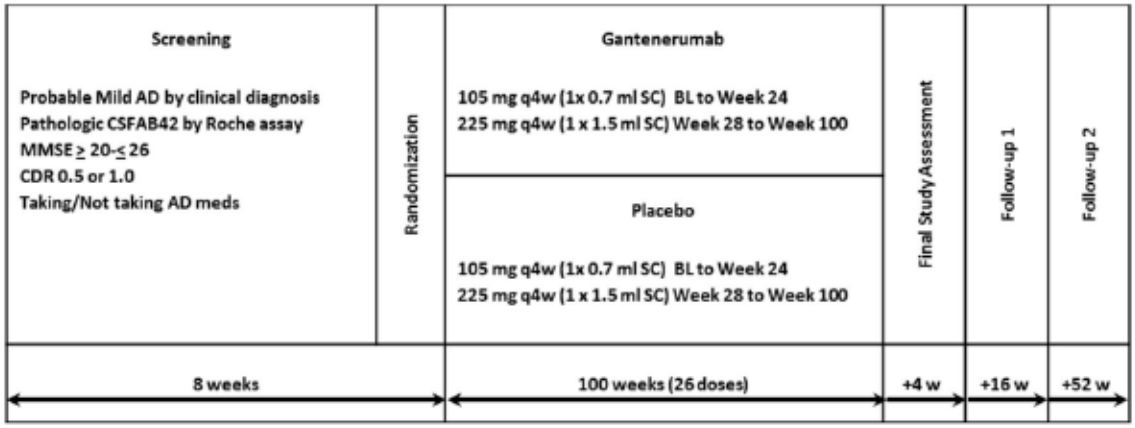
The planned number of patients was approximately 1000 (500 randomized to gantenerumab and 500 to placebo). Patients were assigned to receive gantenerumab or placebo in a 1:1 ratio. Randomization was stratified by geographic region, APOE ε4 status, and use or non-use of anti-dementia medications at baseline in order to maintain a balanced number of patients in each of these strata enrolled in each treatment arm. Approximately 225 centers in approximately 30 countries were to participate.

Patients were eligible for study participation whether or not they were receiving approved symptomatic medications for AD (i.e., ChEIs or memantine; or the medical food supplement Souvenaid®, where approved). Eligible patients were 50–90 years old and at the time of screening, had an MMSE score of 20–26 points, inclusive, a GDS-15 (Geriatric Depression Scale) score <6, and a CDR-GS of 0.5 or 1.0. Patients also had increased brain amyloid, as measured by reduced CSF Aβ1–42.

Neuroradiologic evaluation using a standard MRI protocol and T_2*-weighted gradient-recalled echo (GRE) fluid attenuated inversion recovery MRI as read by the central MRI reader was used to exclude patients with other structural causes of dementia, significant cerebral vascular pathology, more than four microbleeds, and areas of leptomeningeal hemosiderosis combined on a 1.5-Tesla (T) MRI scanner or more than five microbleeds on a 3-T MRI scanner, or evidence of a prior cerebral macrohemorrhage.

Part 1 of the study consisted of a screening period of up to 8 weeks in length for each eligible patient who signed the informed consent and agreed to participate, followed by a double-blind treatment period of 100 weeks and a 52-week follow-up period (see Table 3). For the schedule of assessments, see Appendix 1.

Table 3 Overview of Study Design for Part 1



AD = Alzheimer's disease; BL = baseline; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; MMSE = Mini Mental State Examination; q4w = every 4 weeks.

Eligible patients were randomized to receive gantenerumab or placebo by SC injection q4w for up to a maximum of 100 weeks (26 doses), during which time patients received background treatment for AD according to clinical practice (see Section 3.1.4), followed by a final efficacy and safety assessment 4 weeks following the last dose (Week 104; see Table 3). Patients also had follow-up visits at 16 and 52 weeks after the final dose for safety and limited efficacy (Weeks 116 and 152, respectively). The first course of study drug (Dose 1) was administered on Day 1. The end of the study was considered the Week 152 visit for the last patient enrolled. The primary analysis of safety and efficacy was conducted once the last patient has the Week 104 visit.

Patients who discontinued the study drug prematurely, needed to complete the following visits: early termination visit (4 weeks following the last dose) and two follow-up visits at 16 and 52 weeks after the final dose.

Patients underwent brain MRI exams for monitoring safety and response to study treatment. Patients also underwent common tests of safety, as well as tests of cognition and other clinical scales commonly used in AD clinical trials.

The incidence and nature of adverse events, serious adverse events, ARIA-E and ARIA-H abnormalities, and laboratory abnormalities were assessed on a regular basis by an unblinded iDMC.

Blood samples for assessment of pharmacokinetics and ADA were obtained from all patients.

3.1.2 Study Design in Part 2

All patients (229 patients) who are actively enrolled in Study WN28745 (i.e., not discontinued from study drug) were invited to participate in the OLE study. Double-blind

treatment allocation of patients and APOE ε4 status will be revealed, and the up-titration schedule will be determined depending on APOE ε4 status and whether patients were on placebo or active gantenerumab as per Section 1.4.7.1.

Patients will receive open-label gantenerumab by SC injection q4w for up to an additional 3 years beyond the initial 2 years of OLE, followed by a safety and limited efficacy assessment 4 weeks following the last dose (Follow-Up 1 visit; see schedule of assessments). *The first dose of open-label gantenerumab will be administered after the patient has signed the OLE informed consent form (ICF). Patients will then be given the option of enrolling in an open-label rollover study (WN41874) aimed at evaluating the safety and tolerability of long-term administration of gantenerumab.* Patients *who do not enroll in Study WN41874* will have one additional follow-up visit: Follow-Up 2 at 16 weeks after the final dose for safety and limited efficacy.

Patients will undergo brain MRI exams for monitoring safety and response to study treatment. Patients will also undergo common tests of safety, as well as other cognitive and clinical scales commonly used in AD clinical trials. During the additional years, only the MMSE will be collected as a cognitive scale. ARIA findings will be monitored on an ongoing basis by the Sponsor IMC and an iMRI-C. The iDMC will be reviewing relevant safety findings on a regular basis until the majority of patients have reached the target dose.

Blood samples for assessment of pharmacokinetics and ADA will be obtained from all patients as per OLE Schedule of Assessments.

All patients participating in the associated PET substudies (approximately 100 patients in the WN28745 PET substudy) will also be invited to continue in the substudies to assess changes of brain amyloid load over time with gantenerumab treatment.

In addition to the initial 2 years in OLE, patients will be given the option to continue receiving open-label gantenerumab treatment until the end of 2020.

All patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Patients who discontinue study drug at any time during OLE, or who complete the first 2 years of OLE only will be asked to complete follow-up visits at 4 and 16 weeks from their last dose (Follow-Up 1 and 2, respectively).

3.1.3 WN28745-PET and WN28745 Cardiac PET Substudies

WN28745-PET and WN28745-Cardiac PET are separate substudies to the Phase III main study, WN28745. In the WN28745-PET substudy, patients with mild AD treated (who provide separate informed consent) will undergo yearly PET imaging scans for up to 3 years in OLE using the PET radioligand, a florbetapir F 18 injection, to assess changes in brain amyloid load over time. In the WN28745-Cardiac PET substudy, a subset of these patients at selected centers also had a heart PET scan to measure the

changes in amyloid load in the heart. Five patients were enrolled in the WN28745-Cardiac PET substudy; because none of these patients are in the OLE, the WN28745-Cardiac PET substudy has been stopped.

In consenting patients who are screened for enrollment in the WN28745-PET substudy, qualitative PET scans will also be used to evaluate the concordance between amyloid PET visual read and positivity or negativity of Aβ1–42 CSF testing at study entry (i.e., levels of CSFAβ1–42 below the defined cutoff). Although patients in this study will be selected on the basis of CSF Aβ1–42 below a defined threshold (CSF positive), amyloid PET data in individuals with CSF Aβ1–42 above the threshold (CSF negative) will also be collected. A comparison between the CSF-positive/PET-positive, CSF-positive/PET-negative, CSF-negative /PET-positive, and CSF-negative/PET-negative subgroups will provide an assessment of concordance between the two measurements.

Details about the two substudies are provided in Protocol WN28745-PET and in Protocol WN28745-Cardiac PET.

Patients participating in the OLE and who are already in the PET substudies will be invited to continue with the yearly PET imaging scans for up to 3 years in OLE. If not enrolled in the PET substudies, patients at participating centers may enroll at the start of the OLE into the PET substudy.

3.1.4 Use of Symptomatic Treatments for Alzheimer's Disease

Approved agents for the symptomatic treatment of AD are ChEIs and memantine (and in some jurisdictions, Souvenaid®). In Part 1, patients were eligible for study participation whether or not they were receiving approved medications for AD. If patients were currently receiving approved medications for AD, their doses must have been stable for at least 3 months prior to screening (i.e., 5 months prior to randomization). Every effort should be made to maintain dosing status at entry (i.e., receiving or not receiving background medication) and dosing regimen stable. In Part 2, initiation, dose change, or discontinuation of approved AD treatments is permitted at the discretion of the investigator.

3.1.5 Data Monitoring Committee

During the double-blind part of the study, the incidence and nature of adverse events, serious adverse events, ARIA-E and ARIA-H findings, and laboratory abnormalities were assessed on a regular basis (e.g., quarterly) by an iDMC. The details of the iDMC are documented in the iDMC Charter (available on request).

During the OLE, the iDMC will review safety findings until the majority of patients have reached the target dose. Significant MRI findings during OLE will continue to be reviewed by the IMC and by the iMRI-C as documented in the iMRI-C charter (available

upon request). New relevant findings identified by either the IMC or the iMRI-C may be shared with the iDMC for Phase III Studies WN29922 and WN39658.

3.2 END OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date on which the last datapoint required for safety follow-up is received from the last patient in the OLE. The LPLV is expected to occur *4 or 16 weeks (as applicable)* after the last patient has received their last dose of study drug (i.e., Follow-Up *1 or* 2 visit).

3.3 OPEN-LABEL EXTENSION AND LONG-TERM FOLLOW-UP

Patients who are participating in the OLE will be offered the possibility to continue open-label treatment beyond the initial 2 years (treatment extension). Patients who do not wish to participate in the treatment extension or who discontinue study drug from the OLE at any time will be requested to return for follow-up visits for safety and limited efficacy assessments at 4 and 16 weeks from the time of their last dose of study drug.

3.4 RATIONALE FOR STUDY DESIGN

Part 1 was a Phase III, randomized, double-blind, placebo-controlled study of the efficacy and safety of gantenerumab in patients with a clinical diagnosis of mild AD and increased amyloid burden. The study was of the typical design for mild to moderate AD comparing the change from baseline in two primary endpoints (co-primary), one of them reflecting the cognitive domain and the other reflecting the functional domain of impairment.

Treating patients who have AD with a placebo in the absence of background therapy in clinical trials may raise ethical considerations (Fisk et al. 2007; Zhang et al. 2011); therefore, patients were eligible for study participation whether or not they were receiving approved medications for AD according to the clinical practice of each Principal Investigator.

The planned total number of patients was approximately 1000 (500 patients randomized to gantenerumab and 500 to placebo), which was designed to have at least 80% power at a two-sided α level of 0.05 for testing the hypotheses for each of the co-primary efficacy endpoints using the mixed-effects model repeated measures (MMRM) analysis.

Assessments in clinical trials for AD should be obtained across several domains of neurologic function, including cognition, measured directly by objective tests (cognitive endpoints), and functioning using observational scales for ADL. Improved clinical outcomes in both cognitive and functional domains should translate to an overall benefit measured by a global improvement score, demonstrating that a proportion of patients achieve a clinically meaningful benefit from this therapy. The ADAS-Cog has served as the most widely used primary outcome measure in clinical trials for mild to moderate AD

(Rosen et al. 1984) and is generally considered the gold standard for assessing cognitive function in clinical trials (Cano et al. 2010; Sevigny et al. 2010). The ADCS-ADL consists of measures of basic and instrumental ADL (IADL) and is validated for the assessment of mild to moderate AD and assessments of basic ADL, including self-maintenance skills such as walking, feeding, and dressing, and IADL. The secondary endpoints will be used to monitor additional cognitive, affective, global, and behavioral changes.

Given the results from Study WN25203 and the Prime (aducanumab) studies, this study was converted into an OLE.

3.4.1 Rationale for Key Secondary Endpoints

The key secondary endpoints included the effect of gantenerumab on slowing functional and cognitive decline and disease progression as assessed by confirmed clinical decline on the MMSE and time to loss of ADL, change in the CDR-SB, and ADAS-Cog responder, as well as the effect on biomarkers of disease pathology.

Owing to the mechanism of gantenerumab, the expected effect of treatment is to slow functional and cognitive decline rather than effecting an improvement over baseline. A survival analysis evaluating time to functional decline provides a protocol-specified means to directly assess the impact of gantenerumab in slowing decline on a measure that is considered clinically meaningful.

Functional decline, characterized by the loss of ability to perform ADL, is a common feature of AD that results in growing caregiver burden and the eventual need for alternative care or nursing home placement (Mohs et al. 2001).

Criteria for clinically evident decline in function include either:

- Loss of ≥ 1 points on one or more basic ADL
- Loss of ≥ 2 points on one or more IADL

In addition, loss of ADL, as defined above, must be accompanied by a confirmed decline of ≥ 2 points on the MMSE, which is considered in this case as an indicator of overall general disease deterioration.

Biomarkers to be evaluated included amyloid PET, CSF t-tau and p-tau, and volumetric MRI. Because there is currently no consensus in the clinical community on which biomarker(s) would be appropriate to support clinical findings in trials in early AD, the results of these biomarkers were to be analyzed independently, and without hierarchal structuring, with the understanding that the biomarker findings will be interpreted in the context of the state of the scientific evidence at the time of a potential filing.

3.4.2 Rationale for Study Treatment Duration

For Part 1, the treatment duration of 100 weeks (26 doses) was selected on the basis of the mechanism of action for gantenerumab that was expected to delay disease progression rather than provide symptomatic improvement over baseline. In order to demonstrate this, sufficient time had to elapse for the control group to decline and therefore increase the chance to detect a difference between groups by the end of treatment.

The study duration was consistent with the concept that in mild to moderate AD, long-term placebo-controlled trials are needed; recently completed Phase III trials of anti-Aβ antibodies in mild to moderate AD used study durations of 18 months (approximately 80 weeks).

For the OLE, the initial treatment duration of 100 weeks was selected in order to ensure an appropriate duration for safety monitoring of high doses of gantenerumab and to collect information on potential clinical effects. However, because AD is characterized by progressive decline, it will be important to further characterize the long-term safety of gantenerumab beyond the initial 2 years.

3.4.2.1 Rationale for Duration of Study Follow-Up (16 Weeks)

The primary purpose for the 16-week follow-up visit (i.e., 16 weeks after the last dose) is to evaluate the residual effects of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days and gantenerumab is cleared from plasma after approximately 17 weeks (approximately 5 half-lives). Therefore, safety assessments performed 16 weeks after the last dose are considered sufficient to evaluate residual effects on peripheral safety outcomes. In addition, efficacy assessments at the follow-up visit may support the enduring effect of gantenerumab after treatment is stopped. *The follow-up visit at 16 weeks is not required for patients who enroll in Study WN41874 (open-label rollover study).*

3.4.3 Rationale for Test Product Dose

In Part 1, all patients were initially treated with 105 mg of gantenerumab SC (or placebo) for the first 24 weeks following MRI confirmation supporting the lack of ARIA-E, and no more than one new ARIA-H on MRI after the Week 24 dose, all patients then had the dose increased to 225 mg SC (or placebo) starting with the Week 28 dose (see Section 5.1.4).

In Part 2, dosing will be determined by the patients' carrier status (presence of one or more APOE ε4 alleles = 'carriers' or absence of APOE ε4 allele = 'non-carriers') and their original treatment assignment of placebo or gantenerumab (see Section 1.4.7.1).

3.4.4 Rationale for Patient Population

AD represents a continuum in the severity of cognitive and functional symptoms and the distinction between prodromal and mild AD may be difficult to determine, given that they

are not dichotomous clinical conditions. The core neuropathologic feature of AD–amyloid accumulation in the brain–is present even in the predementia/prodromal stage of the disease continuum. Intervention with a treatment that targets removal of amyloid during the earlier disease stages may demonstrate the greatest clinical benefit and delay the progression in cognitive and functional decline. For this reason, Roche has focused the clinical development of gantenerumab on the prodromal and mild segments of the AD continuum.

As described in Section 1.4.2, further support for targeting prodromal to mild AD comes from recent results from the Phase III clinical studies with the anti-amyloid antibody solanezumab in mild to moderate AD. The Phase III studies failed to meet their primary endpoints, but findings from these studies suggest that anti-amyloid treatments may result in improved clinical outcomes in patients with mild but not moderate AD (Doody 2012). It is therefore reasonable to think that the benefit of anti-amyloid therapy may be greater if initiated early in the disease stage.

Patients enrolled in Study WN28745 will have biomarker evidence of β-amyloid deposition, as demonstrated by decreased levels of Aβ1–42 in the CSF. The use of biomarkers in patient selection in mild AD clinical trials criteria is important because there is accumulating evidence that a significant number of patients enrolled in trials may not have underlying amyloid pathology and therefore may not be suitable for treatment with an anti-amyloid agent. Both the Phase III solanezumab and bapineuzumab programs reported that approximately 20% of their overall respective mild to moderate clinical trial populations did not have amyloid pathology, as assessed on PET (Doody 2012; Sperling et al. 2012a). CSF Aβ1–42 is an indicator of brain amyloid deposition and shows good accuracy in discriminating between individuals with AD from healthy controls (e.g., 96.4% sensitivity and 76.9% specificity in an Alzheimer's Disease Neuroimaging Initiative (ADNI) autopsy-based cohort [Shaw et al. 2009]) and has value in discriminating AD from non-AD dementias (EMA 2012). Because gantenerumab is an anti-amyloid antibody and CSF Aβ1–42 is an indicator of brain amyloid pathology, this biomarker is considered appropriate for selection of patients for gantenerumab treatment based on the mechanism of action of the molecule. Biomarker selection together with the rigorous entry criteria will ensure that individuals with dementia of the Alzheimer's type (i.e., major NCS due to AD) are enrolled in the study.

It is expected that both males and females will be similarly represented in the overall patient population.

3.4.5 Rationale for Biomarker Assessments

The following biomarker assessments will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the clinical trial population.

3.4.5.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Elevated CSF t-tau and p-tau, along with decreased CSF Aβ1–42 levels, are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF Aβ1–42 reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels are reflective of neurodegeneration and tangle formation. Amyloid deposition is considered the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event. Therefore, t-tau and p-tau may be studied as biomarkers downstream of the primary target of anti-amyloid therapies such as gantenerumab.

There is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD from Study AN1792 suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012a). Because no clear evidence of efficacy was demonstrated with these therapies in clinical trials, it is yet to be demonstrated that changes in these biomarkers are linked to a clinically meaningful change in the pathologic processes underlying AD.

Based on these data and on the proposed mechanism of action of gantenerumab, levels of CSF t-tau and p-tau will be assessed at baseline and following treatment. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF Aβ1–42 will also be measured.

3.4.5.2 Brain Volumetry

A characteristic feature of AD is neuronal destruction. Such neuronal loss is demonstrated at a macroscopic level by progressive cerebral atrophy, which can be tracked on MRI (Fox and Kennedy 2009). Multiple changes in brain anatomy beyond those associated with normal aging have been reported in patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (Mungas et al. 2005; Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease progression through longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion being a third and related quantitative marker.

Therefore, to quantify the effects of gantenerumab on neurodegeneration, whole brain volume, ventricular enlargement, and regional brain volume changes will be assessed at

screening and following treatment with gantenerumab. All MRI reads and volume measures will be conducted by the central reader.

In addition to the structural brain volume changes, changes in brain functioning of patients will be assessed using a blood oxygenation level-dependant (BOLD) resting-state fMRI (rs-fMRI) procedure with a paradigm-free procedure (Greicius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of patients with AD contribute to neuronal degeneration in the brain over time that has been found to alter functional connectivity of various brain networks using rs-fMRI (Sheline et al. 2010; Binnewijzend et al. 2012; Brier et al. 2012; Sheline and Raichle 2013). Resting-state functional connectivity has been found to be decreased in brain regions such as the hippocampus, the default mode network (regions such as precuneus, anterior cingulate, and parietal and temporal cortices), and cortical regions in which the functional connectivity is continuously decreased as disease progresses, and found to be decreased in cognitively normal elderly patients with brain amyloid deposition (PiB+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found even after 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity caused by the accumulation of Aβ in the brain.

At sites having the required software and sequence, rs-fMRI (BOLD rs-fMRI) will be performed where feasible during the same scanning session of the structural MRI to assess functional brain connectivity before and after treatment with gantenerumab.

3.5 OUTCOME MEASURES

3.5.1 Primary Efficacy Measures in Part 1

The co-primary efficacy measures for Part 1 of this study were as follows:

- Mean change from baseline at Week 104 in ADAS-Cog13
- Mean change from baseline at Week 104 in ADCS-ADL score

3.5.2 Secondary Efficacy Measures in Part 1

The key secondary efficacy measures for Part 1 of this study were the following:

- Time to clinical decline as measured by

  Confirmed (at two consecutive visits) ≥2-point decline on MMSE, and

  Loss of ≥1 points on one or more basic ADL, as assessed with the ADCS-ADL or

  Loss of ≥2 points on one or more IADL, as assessed with the ADCS-ADL

- Change from baseline at Week 104 in CDR-SB
- ADAS-Cog responder (see the Statistical Analysis Plan for more details)
- Change from baseline (i.e., collected at screening) to Week 104 in CSF t-tau, p-tau, and Aβ1–42 levels

The secondary biomarker outcome measures for this study were as follows:

- Change from baseline (screening visit) to Week 104 in MRI volumetry, as assessed on structural MRI:
  - Change from baseline in hippocampal volume
  - Change from baseline in whole brain volume
  - Change from baseline in cortical thickness
  - Change in baseline in ventricular volume
- Changes in brain and heart amyloid load over time using a florbetapir F 18 injection, a PET radioligand selective to β-amyloid in patients treated with gantenerumab or placebo

Additional secondary efficacy outcome measures for Part 1 of this study were the mean change from baseline at Week 104 in the following:

- CDR-GS
- ADAS-Cog13 scores
- NPI total and domain scores (neuropsychiatric behavior)
- MMSE total score (cognition)
- Clinical composite endpoint (prespecified items from the ADAS-Cog, MMSE, and CDR)
- QoL-AD (global score)
- SymptomGuide™ Facilitated GAS (change in symptoms and goal achievement)
- DS (global score, and Cognitive Support and Assistance and Elder Active scales)
- RUD-Lite (resource utilization, time care-giving, caregiver productivity, and institutionalization)
- ZCI-AD (domains and global scores)

3.5.3 Efficacy Measures in Part 2

3.5.3.1 During the First Two Years

Efficacy measures in Part 2 are exploratory and will include both clinical outcome measures (ADAS-Cog, MMSE, CDR, and ADCS-ADL) and biomarker measures.

3.5.3.2 During the Additional Years

Only the MMSE will be collected during the additional years.

3.5.4 Safety Outcome Measures in Parts 1 and 2

The safety outcome measures for this study are as follows:

- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events
- Incidence, nature, and severity of adverse events
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time and incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Incidence of anti-gantenerumab antibodies
- Physical and neurologic examination abnormalities
- Mean change in vital signs assessment from baseline over time and incidence of abnormal vital signs measurements
- Suicidal ideation, suicidal behavior, and self-injurious behavior without suicidal intent, as determined using the Columbia–Suicide Severity Rating Scale (C-SSRS)

3.5.5 Pharmacokinetic Outcome Measures in Parts 1 and 2

The PK outcome measures for this study are as follows:

- Primary population PK parameters (e.g., apparent total CL [CL/F] and apparent volume of distribution [V/F]) and relevant covariates as necessary to describe the plasma gantenerumab concentration–time course
- Secondary population estimates of plasma gantenerumab exposure at steady state to include peak plasma concentration (C_{max}), time to peak concentration (T_{max}), trough plasma concentration (C_{min}), and AUC

3.5.6 Exploratory Outcome Measures in Parts 1 and 2

The exploratory outcome measures for this study are as follows:

- Change from baseline (screening visit) to Week 104 in functional brain connectivity as measured by rs-MRI

4. MATERIALS AND METHODS

4.1 PATIENTS

Part 1 of this study included patients with a diagnosis of probable mild AD based on NINCDS/ADRDA criteria (McKhann et al. 1984; see Appendix 4) or probable NCD due to AD, mild severity based on the DSM-5 criteria (APA 2013). Patients had an MMSE score of 20 to 26, inclusive, at the time of screening. Patients were eligible for study participation whether or not they were receiving approved medications for AD

(i.e., ChEIs or memantine; Souvenaid®, where approved). If patients were currently receiving medications for AD, doses must have been stable for at least 3 months prior to screening (i.e., 5 months prior to randomization) and as much as possible, dosing regimen stable for at least 6 months after randomization.

Patients who discontinued from this study were not permitted to be enrolled and re-randomized for a second course of treatment or enter the OLE.

4.1.1 Inclusion Criteria in Part 1

Patients must have met the following criteria for study entry:

- Ability to provide written consent signed by the patient (co-signed by the patient's legally authorized representative, if required by the local regulations, guidelines, and independent ethics committee [IEC] or institutional review board [IRB])
- Ages 50–90 years, inclusive
- Clinical diagnosis of probable mild AD based on NINCDS/ADRDA criteria (see Appendix 4) or major NCD due to AD of mild severity based on the DSM-5 criteria whether or not receiving AD approved medication
- If the patient is receiving AD medications, the dosing regimen must have been stable for 3 months prior to screening
- Males and females
- For females 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 or urine tests will be performed for further confirmation of non-childbearing potential if required by local regulations, guidelines, and IRB/IEC
  or
  For females of childbearing potential, a negative urine beta-human chorionic gonadotropin (β-hCG) will be required at screening and baseline, and agreement to use two acceptable forms of effective contraception from the screening visit until 16 weeks after study drug discontinuation as follows:

  Established use of oral, injected, or implanted hormonal methods of contraception

  Intrauterine system or placement of an intrauterine device

  Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam, gel, film, cream, or suppository

  Male sterilization (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).

  True abstinence: Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Availability of a person ("caregiver") who in the investigator's judgment has frequent and sufficient contact with the patient (e.g., ≥10 hours per week of in-person contact), is able to provide accurate information regarding the patient's cognitive and functional abilities, agrees to provide information at clinic visits, which requires partner input for scale completion and signs the necessary consent form

  The caregiver must have sufficient cognitive capacity, in the judgment of the investigator, to accurately report upon the patient's behavior and cognitive and functional abilities. Whenever possible, the caregiver should be the same for the duration of the study.
- Fluency in the language of the tests used at the study site
- Willingness and ability to complete all aspects of the study (including MRI, lumbar puncture, clinical genotyping [see Section 4.5.10], and PET imaging if applicable); the patient should be capable completing assessments either alone or with the help of the caregiver
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Agreement not to donate blood or blood products for transfusion for the duration of the study and for 1 year after final dose of study drug
- Agreement not to participate in other research studies for the duration of this trial and its associated substudies

Cognition-Related and Test-Based Criteria for Mild Alzheimer's Disease

- Screening MMSE score of 20–26 points, inclusive, at screening
- Screening CDR-GS of 0.5–1.0
- Screening GDS-15 score <6
- CSF Aβ1–42 levels ≤700 pg/mL as measured on the Elecsys assay

4.1.2 Exclusion Criteria in Part 1

Patients who met any of the following criteria were excluded from study entry:

4.1.2.1 Central Nervous System Disorders

- Dementia or NCD due to a condition other than AD, including, but not limited to, frontotemporal dementia, Parkinson disease, dementia with Lewy bodies, Huntington disease, or vascular dementia
- History or presence of clinically evident vascular disease potentially affecting the brain (e.g., clinically significant carotid or vertebral stenosis or plaque, aortic aneurysm, intracranial aneurysm, cerebral hemorrhage, arteriovenous malformation) that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of stroke within the past 2 years or documented history of transient ischemic attack within the last 12 months
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)

- History or presence of clinically relevant intracranial tumor (e.g., glioma, cerebral metastasis) that is clinically relevant in the opinion of the investigator
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., syphilis, neuroborreliosis, viral or bacterial meningitis/encephalitis, human immunodeficiency virus [HIV], encephalopathy)
- History or presence of systemic autoimmune disorders potentially causing progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, antiphospholipid antibody syndrome, Behçet disease)
- History or presence of a neurologic disease other than AD that may affect cognition, including, but not limited to, Parkinson disease, corticobasal degeneration, dementia with Lewy bodies, Creutzfeldt–Jakob disease, progressive supranuclear palsy, frontotemporal degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, and hypoxia
- History of schizophrenia, schizoaffective disorder, or bipolar disorder
- At risk of suicide in the opinion of the investigator
- Alcohol and/or substance use disorder (according to the DSM-5) within the past 2 years (nicotine use is allowed)

4.1.2.2 Imaging-Related Criteria

- According to the assessment by the central reader, MRI evidence of a) more than two lacunar infarcts, b) any territorial infarct >1 cm^3, or c) any white matter lesion corresponding to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the fluid attenuated inversion recovery (FLAIR) sequence, which is ≥20 mm in any dimension
- The combined number of microbleeds and areas of leptomeningeal hemosiderosis on MRI is more than four on a 1.5-T machine or more than five on a 3-T machine based on the review performed by the central reader prior to randomization
- Presence of any other significant cerebral abnormalities, including ARIA-E, as assessed on MRI
- Inability to tolerate MRI procedures or contraindication to MRI, including, but not limited to, presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, or foreign metal objects in the eyes, skin, or body that would contraindicate an MRI scan; or any other clinical history or examination finding that, in the judgment of the investigator, would pose a potential hazard in combination with MRI

4.1.2.3 Cardiovascular Disorders

- History or presence of atrial fibrillation (except if only one episode, which resolved more than 1 year ago and for which treatment is no longer indicated), or cardiovascular disorder that in the investigator's judgment poses a risk for future stroke

- Within the last 2 years, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction, angina pectoris, cardiac failure New York Heart Association Class II or higher)
- Uncontrolled hypertension (e.g., blood pressure (BP) generally > 160 mm/Hg systolic or > 95 mmHg diastolic)

4.1.2.4 Hepatic/Renal Disorders

- Chronic kidney disease as indicated by creatinine clearance < 30 mL/min as calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains < 30 mL/min if retested
- Impaired hepatic function as indicated by screening AST or ALT ≥ 2× or total bilirubin ≥ 1.5× the upper limit of normal (ULN), which remains above these limits if retested due to a slightly elevated initial result or abnormalities in synthetic function tests that are judged by the investigator to be clinically significant

4.1.2.5 Infections and Immune Disorders

- History of, or known to currently have HIV infection, hepatitis B or C infection not adequately treated in the opinion of the investigator, or history of spirochete infection of the CNS (e.g., syphilis, Lyme, or borreliosis)
- Systemically, clinically significantly immunocompromised patients, owing to continuing effects of immune-suppressing medication

4.1.2.6 Metabolic and Endocrine Disorders

- Abnormal screening thyroid function tests such that a new treatment or an adjustment of current treatment is required

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for thyroid function.
- Screening folic acid or vitamin B12 levels that are sufficiently low and remain low on retest such that deficiency may be contributing to cognitive impairment or such that the deficiency requires a new treatment or an adjustment of current treatment

  A patient may be rescreened if there is no improvement in cognition after 3 months of adequate treatment.
- Screening hemoglobin A_{1c} (HbA_{1C}) > 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes).

  The patient may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Other Exclusions

- Intellectual disability (static encephalopathy, closed brain injury, mental retardation) that has been excluded by the investigator:

  This may be based on, for example, patient's sufficient education or work experience.

- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture
- Clinically significant abnormal screening blood, urine, or CSF that remain abnormal on retest
- Screening prothrombin time (PT) $>1.2\times$the ULN
- History of cancer except:

  If considered to be cured

  If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, not likely to require treatment in the ensuing 5 years

  For prostate or basal cell carcinoma, no significant progression over the previous 2 years
- Known history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric, human, or humanized antibodies or fusion proteins, including gantenerumab
- Hypersensitivity to any of gantenerumab's excipients
- Any other severe or unstable medical condition not previously mentioned that, in the opinion of the investigator or Sponsor, could be expected to progress, recur, or change to such an extent that it could put the patient at special risk, bias the assessment of the clinical or mental status of the patient to a significant degree, interfere with the patient's ability to complete the study assessments, or would require the equivalent of institutional or hospital care
- Residence in a skilled nursing facility such as a convalescent home or long-term care facility: Patients who subsequently require residence in these facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a caregiver who meets the minimum requirement, as defined in Section 4.1.1.

4.1.2.8 Medication-Related Criteria

The following medications are prohibited for a prespecified duration prior to study start, as indicated, and during the entire period of study participation (patients who start these medications during the study will be withdrawn):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any investigational passive immunotherapy (vaccine) or other long-acting biologic agent that is being evaluated to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment or any other treatment with a monoclonal antibody within 5 half-lives or 3 months of screening, whichever is longer

- Any previous treatment with medications used to treat Parkinsonian symptoms or any other neurodegenerative disorder within 1 year of screening even if the patient is taking the medicine for a non-neurodegenerative disorder such as restless leg disorder
- Typical antipsychotic or a neuroleptic medication within 6 months of screening except as brief treatment for a non-psychiatric indication (e.g., emesis)
- Antihemostasis medications within 3months of screening except for:

  Daily use of aspirin (up to 100 mg/day) or clopidogrel are permitted if stable for the previous 3 months.
- Systemic immunosuppressive therapy including corticosteroids within 3 months of screening or anticipated to be needed during the study
- Chronic narcotic analgesics within 6 months of screening
- Treatment with stimulant medications (e.g., amphetamine, methylphenidate preparations) within 1 month of screening
- Treatment with anticonvulsant medications within 1 month of screening
- Sedative, hypnotic, or benzodiazepine medication within 3 months of screening, except intermittent use of the following for sleep or anxiety:

  Alprazolam, lorazepam, oxazepam, temazepam, diazepam

  A short-acting benzodiazepine-like medication (e.g., zolpidem)

The intermittent use of these medications is permitted, but there should be no use for 4 days prior to any cognitive assessments.

The following medications are permitted if the dose and dosing regimen have been stable for 1 month prior to screening (approximately 3 months prior to randomization) and are expected to remain stable after randomization:

- Prescription medications that might affect cognitive function (e.g., antidepressants, atypical antipsychotic medications)
- Over-the-counter and/or herbal medications, food additive or any other agent or supplement intended to improve cognition or reduce cognitive decline, including, but not limited to, Alzhemed®, ginkgo biloba, huperzine, lecithin, and vitamin B12
- Medications used to treat a mood or anxiety disorder, including selective serotonin reuptake inhibitors, selective norepinephrine reuptake inhibitors, bupropion, buspirone, mirtazapine, or trazodone, given as maintenance treatment
- Medications with anticholinergic activity that may impair cognition or attention (e.g., centrally acting antihistamines, including brompheniramine, chlorpheniramine, dimenhydrinate, diphenhydramine, and doxylamine, or antispasmodic medicines)

Intermittent use of centrally acting antihistamines is permitted, but there should be no use for 4 days prior to any cognitive assessments.

For additional information about concomitant therapies, see Section 4.4.

4.1.3 Eligibility Criteria in Part 2

All patients who have been randomized and are actively participating in the study at the time of the amendment approval in their respective country will be eligible to participate in the OLE. Patients who have been discontinued from the study will not be allowed to enroll in the OLE.

Patients in the OLE will be given the option of extending open-label treatment beyond the initial 2 years.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization in Part 1 was performed centrally using an interactive voice/Web response system (IxRS). After being screened, patients who met all eligibility criteria were randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio was 1 active to 1 placebo. Randomization to treatment allocation was also balanced by geographic region, patient APOE ε4 status, and background medication. Except in circumstances in which a health authority, EC, or IRB required the patient be told of his or her APOE ε4 status, individual patient APOE ε4 status results were blinded to patients, investigators, and the Sponsor in order to maintain the blind in the event that dose reduction is implemented. APOE ε4 status information was supplied directly to the IxRS vendor by the central testing laboratory so that the information could be incorporated at the time of randomization. In cases where APOE ε4 status was already known, the results were blinded to the Sponsor and, as much as possible, to the site and central MRI reader. Patients participating in the PET substudies were also allocated to a study treatment as described above to achieve the 1:1 ratio active to placebo.

Part 1 of the study was conducted in a double-blind manner to minimize potential bias from investigators and patients. The Sponsor was blinded to study treatment. The Master Randomization or Master Medication List was not available at the study center, to Roche monitors, project statisticians, or to the project team at Roche. Unblinding should not have occurred except in the case of emergency situations where knowledge of the study drug assigned would affect patient treatment. The investigator should have made every effort to contact Roche before unblinding a patient. In the event that the investigator unblinded a patient without prior notification, the investigator must have contacted Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study patients for another purpose must have been discussed with Roche.

Because per health authority reporting requirements, the Sponsor was to break the treatment code for all unexpected serious adverse events (see Section 5.7) that are considered by the investigator to be related to study drug.

When required, unblinding was performed by means of an IxRS or an equivalent method. If unblinding was necessary for patient management (in the case of a serious adverse event), the investigator was to break the treatment code by contacting the IxRS. Details about patients whose treatment is unblinded during the study was included in the clinical study report. The password-protected and/or encrypted electronic Master Randomization or Master Medication List was kept by Clinical Supply in a secure system and was only accessible to the Randomization List Managers. No open key to the code was available at the study center, to Roche monitors, project statisticians, or to the project team at Roche. Unblinding for the safety monitoring committee, and PK-PD analysis groups (which are independent of the project team) was performed according to Roche standard procedures.

4.3 STUDY TREATMENT

4.3.1 Formulation, Packaging, and Handling

Gantenerumab is available in the following drug product formulation: G3-2 mL vials (300 mg/vial) from which drug product needs to be withdrawn via a disposable syringe. For higher doses, the study drug can be delivered SC either using multiple syringes, or using a syringe pump. Syringe pumps offer a significant advantage over manual administration because they allow delivering higher volumes of the study drug at a defined injection rate. For the double-blind treatment period, placebo with similar formulation was provided.

All formulations should be stored at 2°C–8°C and protected from light. All drug product solutions should be brought to room temperature prior to administration to minimize discomfort during the injection.

Liquid vials: Gantenerumab must be prepared for dosing under appropriate aseptic conditions as it does not contain antimicrobial preservatives. The dose solution should be used immediately. If not used immediately, the total storage time of the dose solution prior to administration should not exceed 24 hours to limit the risk of microbiological growth in case of accidental contamination. The recommended storage condition for the dose solution is 2°C–8°C, but dose solutions may be stored at room temperature for up to a maximum of 4 hours.

Packaging of the study drug will be overseen by the Roche Clinical Trial Supplies Department and will bear a label with the identification required by local law, the protocol number, study drug identification, and dose. The packaging and labeling will be in accordance with Roche standard and local regulations. Upon receipt of the investigational products at the site, site personnel should check the product for damage and verify the proper identity, quantity, and integrity of the study drug. Site personnel should report any deviations or product complaints to the monitor upon discovery. For further details, please refer to the Gantenerumab IB.

4.3.1.1 Background Treatment for Alzheimer's Disease

In Part 1, patients were eligible for study participation whether or not they were receiving approved medications for AD (i.e., ChEIs or memantine, or the medical food supplement Souvenaid®, where approved). Randomization was stratified for patients taking and not taking approved anti-dementia medications.

In both Part 1 and 2, information on background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) should be captured on the Alzheimer's Medications electronic Case Report Form (eCRF).

4.3.2 Dose, Administration, and Compliance

4.3.2.1 Administration of Investigational Medicinal Product in Part 1

Gantenerumab was administered by SC injection to all patients randomized to the active treatment arm, regardless of APOE ε4 status, at a dose of 105 mg q4w for at least the first 24 weeks and, if eligible, 225 mg q4w from Week 28 to the end of the study. Patients not eligible for titration starting with the Week 28 dose continued to receive 105 mg q4w from Week 28 to the end of the study. Regardless of dose, each patient received up to 26 total injections in the study. Injections were administered as one 0.7- or 1.5-mL SC injection in a 1.0- or 2.25-mL to the abdomen for the 105- and 225-mg doses, respectively.

Placebo of similar physical characteristics and identical volume to gantenerumab was administered by SC injection to all patients randomized to placebo at the same frequency and same route of administration. Patients received one 0.7-mL injection for the first 24 weeks of dosing, and then, if eligible, received one 1.5-mL injection starting with the Week 28 dose until the end of the study. If the patient was not eligible for up-titration, he or she continued to receive one 0.7-mL injection from Week 28 to the end of the study.

On study drug administration days that include efficacy assessments (see Appendix 1 for the schedule of assessments), study drug must have been administered at the clinical site. Study personnel administering study drug must not have been involved with any efficacy assessments or safety evaluations.

On days when only safety is being assessed, there was an option to have study drug administered and applicable safety assessments conducted at a prearranged location away from the study site by a trained health care provider if consent was obtained.

Guidelines for dose modification and treatment interruption or discontinuation are provided in Section 5.1.4.

4.3.2.2 Administration of Investigational Medicinal Product in Part 2

Patients participating in Part 2 will receive open-label gantenerumab extracted from a vial and administered as SC injections to the abdomen every q4w either as one or

multiple injections administered by a syringe or a syringe pump (for 450 mg doses and higher). The titration schedule is described in Section 1.4.7.1.

The gantenerumab 225 and 300 mg dose can be administered subcutaneously by disposable syringe after withdrawal of the HCLF from the vial.

The 450 to 1200 mg doses can be administered subcutaneously using a syringe pump after withdrawal of the HCLF from the vials. These doses can also be administered subcutaneously using one or multiple disposable syringes.

4.3.2.3 Non-Investigational Medicinal Products

In Part 1: Stable (≥3 months prior to screening and approximately 5 months prior to randomization) dose and dosing regimen of approved medications for AD will be permitted at study entry. Dose, dosing regimen, and dosing status at entry (i.e., receiving or not receiving) should remain stable. If start or discontinuation of approved AD treatments or a dose change in an approved AD treatment is deemed necessary by the investigator during the first 6 months after randomization, the patient must be discontinued from the study.

Stable doses of other maintenance medications will also be permitted if not prohibited per the entry criteria. Patients must have been on stable doses of any prescription medications that might affect cognitive function for 1 month prior to screening (approximately 3 months prior to randomization). Medication permissions and prohibitions are described in Section 4.1.2.8.

During the study, patients will be permitted to receive any treatment deemed necessary by the investigator for the management of their disease. However, patients requiring initiation of excluded therapies must discontinue from the study. (Note: Patients who are not receiving anti-dementia medications at study entry and subsequently require such treatments at least 6 months after randomization will be permitted to continue on their randomized treatment and be followed for efficacy and safety assessments.)

In Part 2: Dose, dosing regimen, and dosing status at entry (i.e., receiving or not receiving) should remain stable as much as possible. Stable doses of other maintenance medications will also be permitted. As much as possible, medications should be chosen from the list of permitted medications (as described in Section 4.1.2.8).

4.3.2.4 Compliance

In Part 1, patients who missed more than three consecutive doses for reasons other than safety (see Section 5.1.4) were discontinued from the study for lack of compliance as described in Section 4.7. In Part 2, patients who miss doses due to non-compliance will be allowed to continue in the open label.

4.3.2.5 *PET Tracers*

Participants of the amyloid and tau PET substudies were assessed using PET imaging techniques. According to E.U. guidance, the PET tracers (florbetapir, [18F] RO6958948), as used in the context of these studies, are designated as non-IMP. In some regions, according to local regulations, this PET tracer may be considered to be IMP.

In countries where the PET radioligands are approved for marketing, the approved local product information will be provided, and in countries where they are not approved for marketing, the Investigator's Brochures will be provided.

For the safety reporting requirements dealing with the PET tracers used in this study, refer to Section 5.7.

4.3.3 Investigational Medicinal Product Accountability

All investigational medicinal products (IMPs) required for completion of this study (gantenerumab and placebo) will be provided by the Sponsor. The investigative site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and contents. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed upon by the Sponsor. The site must obtain written authorization from the Sponsor before any IMP is destroyed, and IMP destruction must be documented on the appropriate form.

Accurate records of all IMPs received at, dispensed from, returned to, and disposed of by the study site should be recorded on the Drug Inventory Log.

4.3.4 Post-Trial Access to Gantenerumab

This study will be ending in 2020. Patients who are still receiving study treatment at the end of the study will be given the option of enrolling in Study WN41874, the open-label rollover study aimed at evaluating the safety and tolerability of long-term administration of gantenerumab.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by a patient 6 months prior to screening to the study completion/early termination visit. All concomitant medications should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Dosing status at entry in Part 1 (i.e., receiving or not receiving background AD medication or permitted medication listed in Section 4.1.2.8), dose, and dosing regimen should remain stable for at least 6 months after randomization. Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted under the specifications listed below:

- Anticonvulsant medications for an approved pain indication
- SSRIs for the treatment of depressive symptoms
- As-needed use of narcotic analgesics (up to a maximum of 3 consecutive days per month) except in the 4 days prior to any cognitive assessments
- Alprazolam, lorazepam, oxazepam, or temazepam, or a one-time dose of diazepam or a short-acting benzodiazepine-like medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except in the 4 days prior to any cognitive assessment.
- One-time dose of benzodiazepine for presurgical and preimaging sedation at appropriate visits
- Intermittent use of centrally acting antihistamine medications except in the 4 days prior to any cognitive assessment
- Under certain circumstances, initiation of antihemostasis medications may be permitted during study conduct:

    Daily use of either aspirin (up to 100 mg/day) or clopidogrel [in response to an emerging adverse event]

    Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery). In these circumstances, appropriate safety assessments should be made, if occurring prior to a lumbar puncture. The investigator should discuss with the Sponsor all individual cases which require anticoagulant therapy.

Concomitant and excluded therapies for determination of patient eligibility are described in Section 4.1.2.8.

In Part 2, the dose and dosing regimen of permitted medications should, as much as possible, remain stable. Adding a new medication for the treatment of an adverse event should be at the Principal Investigator's discretion. Whenever possible, a permitted medication should be used if appropriate.

4.5 STUDY ASSESSMENTS

The study assessments are detailed in the following sections. Please see Appendix 1 for the schedule of assessments performed during Part 1 of the study and Appendix 2 for the assessments performed during Part 2.

4.5.1 Informed Consent Forms and Screening Log

All patients and caregivers must review, sign, and date the most current IRB/IEC-approved written informed consent form(s) before any study-specific assessments or procedures are performed.

Where approved as per local regulations, the patient's legally authorized representative (LAR) may sign/co-sign the ICF if the patient is no longer able to provide consent. However, patients will need to provide assent that should be documented at the site level. Patients who do not sign the most current ICF will be discontinued from the study.

4.5.2 Medical History and Demographic Data

Medical history and personal status includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse, and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 6 months prior to the screening visit. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurologic systems and will be performed as part of the screening physical exam. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

At subsequent visits, per the schedule of assessments (or as clinically indicated), limited, symptom-directed physical examinations should be performed. Change from baseline abnormalities should be recorded in the patient's notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

A physical exam is not required prior to the OLE unless deemed necessary by the Principal Investigator. A physical exam will be required at the end of the open-label treatment or in case of early withdrawal.

4.5.4 Vital Signs

Vital signs (systolic and diastolic BP, heart rate, and temperature) will be measured as per the schedule of assessments. BP and heart rate should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all BP measurements.

Heart rate will be determined by radial pulse and will be recorded as beats per minute. The pulse should be counted for a minimum of 20 seconds at each measure.

4.5.5 Cognitive Assessments

Cognition will be assessed using the ADAS-Cog13 and MMSE.

The cognitive assessments described in this section will be performed in the order specified in Sections 4.6.1 and 4.6.2 and the schedule of assessments (see Appendix 1).

The scales and assessments for this study will be provided unless otherwise specified. Whenever possible, there should be consistency in the rater and caregiver completing the scales for each patient throughout the duration of the study. Potential raters will need to receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments/rating scales in the study. Raters who are rating secondary scales do not need approval but do need to have completed appropriate training. In addition, given that the primary outcome measure in this trial involves subjective judgment, the adequacy of patient interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale CRO and is considered to be an essential part of good research methodology. Prior studies have clearly demonstrated that the failure to adequately monitor such ratings can substantially increase the risks of failed trials (Becker and Greig 2008; Kobak 2010).

4.5.5.1 Alzheimer's Disease Assessment Scale-Cognition

The ADAS-Cog (Rosen et al. 1984) is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD. The modified version will be used, which has 13 items and includes the addition of 1) delayed word recall, and 2) number cancellation, as well as use of only one trial for word recognition. Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.2 Mini Mental State Examination

The MMSE is a set of standardized questions used to evaluate possible cognitive impairment and help stage the severity level of this impairment. The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities.

4.5.6 Other Clinical Assessments

4.5.6.1 Alzheimer's Disease Cooperative Study–Activity of Daily Living Scale

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in patients with AD (Vellas et al. 2008). The ADCS-ADL covers both basic ADL (e.g., eating and toileting) and more complex ADL or IADL (e.g., using the telephone, managing finances, preparing a meal). IADLs are more sensitive in the mild AD population compared with basic ADLs.

4.5.6.2 Clinical Dementia Rating Scale

Washington University's CDR is a global assessment instrument that yields global GS-SB scores. The CDR-SB score is a detailed quantitative general index that provides more information than the CDR-GS in patients with mild dementia (O'Bryant et al. 2010). The CDR characterizes six domains of cognitive and functional performance applicable to AD and related dementias: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. The necessary information to make each rating is obtained through a semi-structured interview of the patient and a reliable informant or collateral source (e.g., family member). Details of the CDR can be found at the website: http://alzheimer.wustl.edu/cdr/cdr.htm.

As much as feasible, the CDR should be administered to an individual patient by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, or ADCS-ADL. However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR patient interview must be performed any time after the MMSE.

4.5.6.3 Clinical Composite Endpoint

The clinical composite endpoint is a combination of cognitive, global, and functional prespecified items from ADAS-Cog, MMSE, and CDR that measure both cognitive and functional or global deterioration. It is not a stand-alone battery but rather a derived composite that includes four ADAS-Cog items (recall, delayed recall, orientation, word finding difficulty), one MMSE item (orientation to time), and all six CDR items (personal care, community affairs, home and hobbies, judgment and problem solving, memory, orientation). The clinical composite may be more sensitive in detecting a treatment effect for a disease-modifying treatment than each of the items individually; however, the composite score requires validation for use as a primary endpoint in a clinical trial.

4.5.6.4 Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) (Cummings et al. 1994; Cummings 2009) 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 that evaluates 12 neuropsychiatric disturbances common in dementia: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria,

disinhibition, aberrant motor behavior, night-time behavioral disturbances, and appetite and eating abnormalities. The severity of each neuropsychiatric symptom is rated on a 3-point scale (mild, moderate, and marked) and the frequency on a 4-point scale (occasionally, often, frequently, and very frequently). The caregiver distress portion of the scale will not be used in this study.

The NPI will not be collected in the OLE.

4.5.6.5 Geriatric Depression Scale

The GDS is used for quick screening for depression in a high-risk population. The GDS is specifically developed for use with older people and it contains few somatic items. It has been extensively used in communities, acute-care, and long-term care settings. The scale consists of 15 questions that are answered yes or no on the basis of how the patient felt over the past week. Total scores of 0–5 are considered normal and scores of 6–15 are considered depressed.

The GDS will be administered at the screening visit with results being used as part of the inclusion criteria.

4.5.6.6 Columbia–Suicide Severity Rating Scale

The C-SSRS (http://www.cssrs.columbia.edu) is an assessment tool used to assess the lifetime suicidality of a patient (C-SSRS at 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.

The C-SSRS will be conducted at visits, as indicated in the schedule of assessments. The assessment will be completed by a certified C-SSRS rater after interviewing the patient and the patient's caregiver when in attendance at the visit.

During the OLE, the C-SSRS will be collected every 6 months. Additional C-SSRS may be collected as deemed necessary by the Principal Investigator.

4.5.6.7 Patient- and Caregiver-Reported Outcomes

A patient-reported outcome (PRO) is defined as a measurement of any aspect of a patient's health status that comes directly from the patient, without interpretation of his or her comments.

A caregiver-reported outcome is defined as an assessment of observable aspects of the patient's health status assessed by the caregiver without interpretation by the site (DS). In addition, measurement of concepts relevant to the caregiver's health status that is made by the caregiver without interpretation by the site (ZCI-AD) falls within this umbrella term. A caregiver is defined as a person who in the investigator's judgment has frequent and sufficient contact with the patient (e.g., ≥10 hours per week of

in-person contact) so as to be able to provide accurate information as to the patient's cognitive and functional abilities, who agrees to provide information at clinic visits that require partner input for scale completion, and who signs the necessary consent form.

The caregiver-reported outcome instruments and patient-reported outcome instruments, adequately translated and adapted for the local language and culture according to the International Society of Pharmacoeconomics and Outcomes good principles (Wild et al. 2005), will be distributed by the investigative staff and completed in its entirety by the designated responder.

Adverse event reports will not be derived from patient- or caregiver-reported outcome data. Refer to Section 5.3.5.13.

In this study, patient- and caregiver-reported outcomes instruments will be completed in the order specified in Sections 4.6.1 and 4.6.2 and as specified in the schedule of assessments (see Appendix 1).

No patient and/or caregiver reported outcome measures will be collected during the OLE.

4.5.6.7.1 Dependence Scale

Dependence has been shown to strongly correlate with changes in physical functioning and simultaneously associated with cognition and behavior (Spackman et al. 2013).

The DS was originally developed as an instrument to capture a caregiver's report of the level of dependence of patients with AD (Stern et al. 1994). Part 1 consists of 13 questions assessing the patient's level of independence across the continuum of AD, including cognitive support (e.g., need for reminders) and support in instrumental and basic ADL (e.g., driving, mobility) while Part 2 assesses equivalent institutional care. Part 2 will not be used in the study. The DS is scored by summing the scores from each item in Part 1 to derive three domain scores and a total score, with higher scores indicating of greater dependence by the patient. The instrument will be completed on paper.

The DS will not be collected during the OLE.

4.5.6.7.2 Zarit Caregiver Interview for Alzheimer's Disease

The ZCI-AD was adapted from the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers of people with dementia (Zarit and Zarit 1990). A modified version was developed with Dr. Zarit to optimize the scale sensitivity and acceptability. Changes include slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the patient, removal of "burden" from title) and use of 11-point numerical rating scales instead of a 5-point Likert-type scale. Few items were added on the basis of concepts that were deemed

important by caregivers to better characterize the effect of the patient's functional or behavioral impairments on a caregiver's life, including the home care situation.

The modified scale consists of a total of 30 items and captures the following concepts: dependence, worry, emotional well-being, physical health, impact on social and family life, loss of control, financial impact, and overall burden. Total and domain scores will be calculated (higher scores indicate higher levels of distress). Documentation of the questionnaire's psychometric properties will be performed as exploratory analyses.

The ZCI-AD will be completed on paper. If a patient's caregiver is replaced during the study, the ZCI-AD will not be completed by his or her new caregiver.

The ZCI-AD will not be collected during the OLE.

4.5.6.8 Quality of Life–Alzheimer's Dementia

The QoL-AD was developed to assess QoL in patients who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items assessing concepts aligned with the World Health Organization's (WHO) QoL definition: patients' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL (WHO 2008; WHO and Alzheimer's Disease International 2012). Items are rated on 4-point Likert-type scales.

In this study, the QoL-AD will be administered on paper, in a standardized, structured interview format to the patient and caregiver by investigative staff in order to gather patient responses on QoL rather than proxy responses from the caregiver. A global score is generated, with a higher score indicating better QoL. The Caregiver Questionnaire will not be completed.

The QoL-AD will not be collected during the OLE.

4.5.6.9 SymptomGuide™ Facilitated Goal Attainment Scaling

The SymptomGuide™ is an individualized Internet-based technology platform that allows patients with the support of their caregiver to select symptoms associated with dementia that are the most important for them and track their changes in severity and frequency over the course of the trial. In addition, the SymptomGuide™ facilitates use of the GAS by recording symptoms that represent goal areas to be targeted for improvement; the descriptors facilitate both the baseline description (i.e., the level coded 0 at baseline) and the descriptions of the various attainment levels (i.e., the −2, −1 and +1, +2 levels) for each goal. GAS is a method originally developed for adults in the mental health arena as a program evaluation tool that facilitates patient participation in the goal-setting process (Kiresuk et al. 1994). GAS provides a means to identify intervention outcomes that are specifically relevant to individuals and their families. Through the use of the SymptomGuide™ during goal-setting and post-treatment

sessions, the GAS process captures functional and meaningful aspects of a person's progress that are challenging to assess using available standardized measures.

The SymptomGuide™ Facilitated GAS will be conducted at investigational sites in French- and English-speaking countries to document which symptoms of dementia are of most importance for patients and assess achievement of patient-individualized goals. The SymptomGuide™ will be completed by the patient, with support of the patient's study partner and investigative staff.

The GAS will not be collected during the OLE.

4.5.6.10 Resource Utilization in Dementia Scale

The RUD-Lite (Version 3.2) is a shorter version of the Resource Utilization in Dementia scale (Wimo et al. 2003) that aims to document formal and informal resource use in a clinical trial setting. The RUD-Lite captures the most important elements in dementia care: accommodation, informal care, hospitalizations, and community care services. Information on caregiver sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, IADL, and supervision. Data on accommodation and temporary changes in accommodation during the last month and the duration of these will be collected according to four levels of accommodation: own home, intermediate forms of accommodation, dementia-specific residential accommodation, and nursing home. Resource utilization will be collected as the number of nights spent in different types of hospital wards, the number of visits to the most common types of outpatient care, and the number of visits in community care services. Caregivers will complete the scale on paper.

The RUD-Lite will not be collected during the OLE.

4.5.6.11 Electronic Assessment of Rating Scales

The following rating scales will be captured electronically and transferred to the database directly from the core laboratory: ADAS-Cog, ADCS-ADL, CDR, MMSE, and SymptomGuide™ Facilitated GAS.

During the OLE additional years, the MMSE will be collected as a paper-and-pencil scale.

4.5.7 Laboratory Assessments

Samples for the following laboratory tests will be sent to a central laboratory for analysis. Instruction manuals and supply kits will be provided for all central laboratory assessments.

The total volume of blood drawn for laboratory assessments in Part 1 was approximately 130–232 mL during the study (<2 years) and no more than 23 mL at any one visit. For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

The total volume of blood drawn for laboratory assessments during the first 2 years in Part 2 will be approximately 99–154 mL. Starting in Year 3, the scheduled yearly total volume will be approximately 20 mL.

Serum Chemistry: AST/ SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory)

HbA_{1C}, folic acid, and vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed as per the schedule of assessments.

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

Coagulation: 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 patient eligibility pertaining to drugs of abuse. Inconclusive results may be repeated once during the screening period. Investigators should use their best clinical judgment in cases where results may be erroneous (e.g., permitted use of opiates or ingestion of food/food supplements).

Urinalysis: At screening only, urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination will be performed by the central laboratory if blood and/or protein results are positive or strongly positive.

Urine for Pregnancy: Urine pregnancy testing will be performed at each dosing visit for women of childbearing potential (including those who have had a tubal ligation), and at the site for any other female participants if required by local regulations. Women who are of childbearing potential must have a pregnancy test conducted by the site study team prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

4.5.8 Biomarker Sampling

Samples will be collected from all patients 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 AD and related diseases. *Any unused sample material collected for PK and ADA testing throughout the duration of the study may also be used for exploratory biomarker purposes as described in this section.*

4.5.9 Cerebral Spinal Fluid Sampling

CSF samples will be collected according to the schedule of assessments. In Part 1, CSF samples were mandatory at screening and Week 104; collections at Weeks 52 and 152 were optional. Optional CSF samples will be collected during the first 2 years of Part 2 only. Lumbar puncture will be performed by an individual who meets all local requirements and is proficient in the procedure. Lumbar puncture procedures and post–lumbar puncture care will be performed in accordance with local practice. CSF sampling should be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. 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 onsite and used for the following:

- Local laboratory testing for cell count (erythrocytes and leukocytes, with differential if the count is abnormal)
- Central measurement of gantenerumab levels in the CSF (see Section 4.5.14.1) and biomarker analysis, including Aβ1–42, t-tau, p-tau, and tentatively, Aβ1–40. This sample may also be used to support the development of biomarker assays for patient selection/stratification (i.e., Aβ1–42, t-tau, and p-tau).

Normal ranges for CSF cell counts will be sent to the Sponsor by the site for data entry. Unused CSF samples (up to 6 mL) will be kept for future biomarker research if the patient gives consent to the RCR (see Section 4.5.15). Unused sample material may also be used for the purposes of current assay improvement. The procedures for handling and shipping of CSF samples for biomarker analyses are specified in the Sample Collection, Handling, and Logistics Manual.

4.5.10 Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every patient who has consented to participate in the study. All patients will be evaluated for APOE ε4 status and Fcγ receptor genotype. The Fcγ receptor genotype may play a role in PK and PD variability of antibody-based therapeutic agents and may be predictive of response/non-response.

Note: If not already known, the APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and patient and will not be shared with the investigator or the patient until the study is unblinded (unless required for patient safety or by the relevant

health authority or IRB/EC). Patients will have access to this information if they elect to at the end of the study. If already known, the APOE ε4 status will still need to be confirmed and should be kept blinded from the Sponsor. In addition, as much as possible, the status should remain blinded to the site and central MRI readers.

In Part 2, the APOE ε4 carrier status (carrier or non-carrier), as well as the originally assigned treatment arm (placebo or gantenerumab) may be revealed to patients and investigators and will be used to determine the speed of up-titration to the target dose. The number of APOE ε4 alleles will not be revealed to patients unless required by health authority, EC, or IRB. Appropriate counseling will be available at the site level to provide education around the clinical meaning of having 'carrier' or 'non-carrier' status to patients and their families.

The procedures for the collection, handling, and shipping of clinical genotyping samples are specified in the Sample Handling and Logistics Manual.

4.5.11 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all patients as noted in the schedule of assessments (see Appendix 1 for Part 1 and Appendix 2 for Part 2).

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 obtained for PK and ADA assessments will be approximately 85 mL. During the first 2 years in Part 2, the total volume of blood obtained for PK and ADA assessments will range from 99 to 154 depending on patients' carrier status and prior treatment assignment during the double-blind phase. Starting Year 3 of the OLE, scheduled yearly blood volume for PK and ADA sampling will be approximately 7 mL.

Samples collected 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 ADA assay improvement. *Leftover plasma ADA samples may also be used for exploratory biomarker analysis, which may include, but is not limited to, biomarkers of neuropathology (e.g., Ab42, Ab40, tTau, pTau, neuroinflammation [for example, YKL40], and neurodegeneration [for example, NFL]). These leftover samples will be destroyed no later than 5 years after the study results have been reported.*

4.5.12 Electrocardiograms

After 5 minutes in a supine position, a single 12-lead ECG read will be performed at the timepoints indicated in schedule of assessments (see Appendix 1 for Part 1 and Appendix 2 for Part 2). Body position should be consistently maintained for each ECG

evaluation to prevent changes in heart rate. Environmental distractions (e.g., television, radio, conversation) should be avoided during the pre-ECG resting period and during ECG recording.

All ECGs will be recorded/digitized using a validated device provided by the Sponsor or Sponsor delegate. ECGs for each patient should be only be obtained from this machine. On visits where ECGs and other laboratory assessments are performed, ECGs should be performed prior to any blood draws, brain MRI scans, and lumbar puncture. All ECGs will be read by a central reader. ECG characteristics, including heart rate, QRS duration, and RR, PR, and QT intervals, will be transferred to the database directly from the core laboratory. The investigator or his or her designee must review the outputs to ensure there are no clear alerts for quality or clinical issues and then sign and date the outputs.

4.5.13 Brain Magnetic Resonance Imaging

The MRI should be performed using 1.5-T or 3.0-T scanners, and the same scanner should be used for an individual patient for the full duration of the study. MRI will be conducted at patient screening for safety monitoring, as a baseline measure of structural brain volumes and fMRI outcome measures, and as baseline information for the PET substudy concordance analysis (for the schedule of assessments, see Appendix 1 for Part 1 and Appendix 2 for Part 2). In addition, the screening MRI will be used to help determine whether the exclusion criteria are met (e.g., number of microbleeds, presence of mass lesions, etc.). MRI will be used during the study to help assess safety such as the occurrence of microbleeds or signs potentially indicative of inflammation or ARIA-E. Additional unscheduled MRI scans may be utilized to better understand relevant CNS-related adverse events (such as increased confusion) or to follow a sign that emerges 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 patient according to local standards. Finally, structural MRI (to assess whole brain and regional brain atrophy) and fMRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (as per the schedule of assessments).

MRI scans will include the following sequences:

- 3D T_1-weighted GRE scans
- T_2*-weighted GRE scans
- T_2-weighted FLAIR scans
- BOLD rs-fMRI, if available (to assess resting-state functional connectivity at investigative sites having the required software/sequences)

The MRI will take approximately 45 minutes to complete.

The MRI should not be performed unless at least 3 days have passed since a lumbar puncture. If an MRI and lumbar puncture are both scheduled for the same day, the MRI

should be performed first. Within 7 days prior to the scheduled MRI visit, site staff should contact the patient or caregiver to prospectively determine whether the patient is experiencing any CNS-related symptoms.

All images (except BOLD fMRI) will be used to assess MRI inclusion and exclusion criteria.

The MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessment of MRI outcome measures. MRI scans should preferably be transferred to the central MRI core laboratory electronically. Data transfer from individual study sites to the central MRI core laboratory may take up to 7–10 days, if not done electronically. Upon receipt of the MRI scans from the study sites, the central MRI core laboratory will provide the diagnostic reads. MRI results must be made available to investigators prior to next dosing.

MRI facility qualification and scan quality control will be performed by the central MRI core laboratory.

Additional instructions regarding the procedures for MRI facility qualification and MRI scan acquisition and transmittal to the central reading facility can be found in the MRI Manual.

4.5.13.1 Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

As part of site qualification, one to two volunteers (preferably two) at each site should be recruited and scanned using the same machine and the same sequences to be used for site qualification before any patient is scanned in this study. The choice of healthy volunteers is at the discretion of the Principal Investigator and/or the imaging center, and the volunteer must provide written consent to take part in the scanning calibration. 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 or 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 additional scans with the same volunteer acquired after certain events as follows: at the time of a major upgrade to the site's scanner, 4 months without any patient scans occurring at a site, or any other event deemed significant enough to affect image quality. 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.

4.5.14 Pharmacokinetic Sampling

4.5.14.1 Plasma Gantenerumab

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of assessments. An additional PK sample for the

assessment of plasma concentrations of gantenerumab will be obtained as soon as is practical (e.g., at an unscheduled visit or at the next scheduled visit) once the site becomes aware of the occurrence of a symptomatic ARIA-E or an ARIA-E with BGTS ≥4, a worsening of ARIA-E (>2 cm during the double blind; or BGTS ≥4 during the OLE), or ARIA-H meeting the criteria for discontinuation.

Samples from patients receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analyzed in real time, but will be batched for analysis at or near study completion.

Unused sample material may also be used for the purposes of current assay improvement. *Leftover plasma PK samples may also be used for exploratory biomarker analysis, which may include, but is not limited to, biomarkers of neuropathology (e.g., Ab42, Ab40, tTau, pTau, neuroinflammation [for example, YKL40], and neurodegeneration [for example, NFL]). These leftover samples will be destroyed no later than 5 years after the study results have been reported.*

4.5.14.2 Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration

An aliquot of CSF obtained by lumbar puncture as detailed in Section 4.5.9 will be allocated for the measurement of gantenerumab concentration. Samples from patients receiving placebo may not be assessed at once in the first instance, but will be retained for subsequent analysis if appropriate.

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

4.5.15 Samples for Roche Clinical Repository

4.5.15.1 Overview of the Roche Clinical Repository

The RCR is a centrally administered group of facilities used for the long-term storage of human biologic specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection and analysis of RCR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for patients in the future.

RCR specimens will be used to achieve the following objectives:

- To study the association of biomarkers with efficacy, adverse events, or disease progression
- To increase knowledge and understanding of disease biology
- To study drug response, including drug effects and the processes of drug absorption and disposition
- To develop biomarker or diagnostic assays and establish the performance characteristics of these assays

No additional RCR samples will be collected in Part 2.

4.5.15.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RCR is contingent upon the review and approval of the exploratory research and the RCR portion of the Informed Consent Form by each IRB/Ethics Committee (EC) and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RCR sampling, this section of the protocol (Section 4.5.15) will not be applicable at that site.

4.5.15.3 Sample Collection

Three types of samples will be collected for identification of dynamic (non-inherited) biomarkers by the RCR: CSF, plasma, and RNA.

- Analysis of plasma and CSF samples may be used for exploratory biomarker assays, including but not limited to determination of markers of amyloid deposition and/or clearance, markers of oxidative stress, neurodegeneration, inflammation, or other processes implicated in the pathogenesis of AD.
- RNA samples may be tested using techniques such as high-density microarray profiling and/or quantitative reverse transcription polymerase chain reaction (qRT-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.
- 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.

The following sample types will be assessed from consenting patients:

- DNA: DNA samples may be used to explore the associations of variants of genes implicated in susceptibility and pathogenesis of AD, such as, but not limited to, clusterin and phosphatidylinositol-binding clathrin assembly protein (PICALM), and therapy response.
- RNA: RNA samples may be tested using techniques such as high-density microarray profiling and/or qRT-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.
- Plasma: Plasma samples may be used for exploratory biomarker assays, including, but not limited to, markers of oxidative stress, neurodegeneration, inflammation, or other processes involved in AD.
- CSF: Samples remaining from the mandatory analysis will be stored as RCR samples for future exploratory analysis, such as, but not limited to, assessment of biomarkers of inflammation, neurodegeneration, oxidative stress, or other processes thought to be involved in the pathogenesis of AD, and to support the development of biomarker and diagnostic assays.

For all samples, dates 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 the Sample Handling and Logistics Manual.

RCR specimens will be destroyed no later than 15 years after the date of final closure of the associated clinical database. The RCR storage period will be in accordance with the IRB/EC-approved Informed Consent Form(s) and applicable laws (e.g., health authority requirements).

The dynamic biomarker specimens will be subject to the confidentiality standards described in Section 8.4. The genetic biomarker specimens will undergo additional processes to ensure confidentiality, as described below.

4.5.15.4 Confidentiality

Given the sensitive nature of genetic data, Roche has implemented additional processes to ensure patient confidentiality for RCR DNA specimens and associated data. Upon receipt by the RCR, each blood sample for DNA isolation or DNA will be "double-coded" by replacing the patient identification number with a new independent number. Data generated from the use of these specimens and all clinical data transferred from the clinical database and considered relevant will also be labeled with this same independent number. A "linking key" between the patient identification number and this new independent number will be stored in a secure database system. Access to the linking key is restricted to authorized individuals and is monitored by audit trail. Legitimate operational reasons for accessing the linking key are documented in a standard operating procedure. Access to the linking key for any other reason requires written approval from the Pharma Repository Governance Committee and Roche's Legal Department, as applicable.

Data generated from RCR specimens must be available for inspection upon request by representatives of national and local health authorities, and Roche monitors, representatives, and collaborators, as appropriate.

Patient medical information associated with RCR specimens is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Data derived from RCR specimen analysis on individual patients will generally not be provided to study investigators unless a request for research use is granted. 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 data will become and remain the exclusive and unburdened property of Roche, except where agreed otherwise.

4.5.15.5 Consent to Participate in the Roche Clinical Repository

The Informed Consent Form will contain a separate section that addresses participation in the RCR. The investigator or his or her authorized designee will explain to each patient the objectives, methods, and potential hazards of participation in the RCR. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to provide optional RCR specimens. Patients who decline to participate will not provide a separate signature.

The investigator should document whether or not the patient has given consent to participate by completing the RCR Research Sample Informed Consent eCRF.

In the event of an RCR participant's death or loss of competence, the participant's specimens and data will continue to be used as part of the RCR research.

4.5.15.6 Withdrawal from the Roche Clinical Repository

Patients who give consent to provide RCR specimens have the right to withdraw their specimens from the RCR at any time for any reason. If a patient wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the patient's wishes using the RCR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RCR Research Sample Withdrawal Informed Consent eCRF. The patient will be provided with instructions on how to withdraw consent after the trial is closed. A patient's withdrawal from Study WN28745 does not, by itself, constitute withdrawal of specimens from the RCR. Likewise, a patient's withdrawal from the RCR does not constitute withdrawal from Study WN28745.

4.5.15.7 Monitoring and Oversight

RCR specimens will be tracked in a manner consistent with Good Clinical Practice by a quality-controlled, auditable, and appropriately validated laboratory information management system to ensure compliance with data confidentiality as well as adherence to authorized use of specimens as specified in this protocol and in the Informed Consent Form. Roche monitors and auditors will have direct access to appropriate parts of records relating to patient participation in the RCR for the purposes of verifying the data provided to Roche. The site will permit monitoring, audits, IRB/EC review, and health authority inspections by providing direct access to source data and documents related to the RCR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled patients and for patients who are not subsequently enrolled will be maintained at the study site.

After giving written informed consent, patients who are willing to participate in the study will undergo thorough screening assessments up to 8 weeks prior to the baseline visit, as detailed in the schedule of assessments. Patients must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit. In case of an abnormal laboratory or ECG result at screening that may normalize upon retest, investigators have the option to repeat the tests (prior to baseline and within the 8-week screening window) one time to confirm the test results before randomizing a patient at baseline.

In rare cases in which a MRI scan 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 must be approved by the Sponsor and should be in exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of assessments/rating scales at screening is as follows:

Patient	Caregiver
MMSE	CDR (caregiver input)
CDR (patient interview)	ADCS-ADL
ADAS-Cog13	
GDS	

ADAS-Cog13=Alzheimer's Disease Activity Scale–Cognitive (subscale) 13; ADCS-ADL=Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR=Clinical Dementia Rating; GDS=Geriatric Depression Scale; MMSE=Mini Mental State Examination.

If a patient does not qualify on the basis of applicable tests, the patient may be rescreened again after at least 3 months have elapsed if recruitment for the study is still ongoing (see Section 4.1.1, Inclusion Criteria).

As noted in the exclusion criteria (see Section 4.1.2.6), patients may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B12, or HbA_{1C} results.

Patients may be rescreened if the protocol is amended such that they would satisfy the amended criteria and if recruitment for the study is still ongoing. In this case, all

screening assessments must be repeated other than the lumbar puncture and CSF testing if performed within the previous 12 months for this study.

Patients may be rescreened if there is a substantial change in the patient's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing.

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

It is suggested that the remaining screening tests with the exception of the lumbar puncture and MRI (and PET scan if a patient is enrolled in any of the WN28745-PET substudies) be done within 1 to 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 patient from the trial, the CSF collection and MRI scan should be done. If the patient has had a brain MRI scan within the last 6 months as part of the evaluation of cognitive impairment, and if the scan did not have any findings that would exclude the patient from the study, the CSF results can be obtained prior to the screening MRI being performed and the screening MRI should then be done only after it is known that the CSF results satisfy the eligibility criteria. If no recent scan is available, then it is suggested that the MRI should be done first and the lumbar puncture done after it is known that the MRI scan satisfies the selection criteria unless in the opinion of the investigator there is sufficient reason that the lumbar puncture should be done prior to MRI.

It will 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 patients in any of the PET substudies, scans can be obtained after all other screening results are available, with the exception of MRI and CSF results. PET may be performed after the lumbar puncture and prior to when CSF results are received; there is no requirement for CSF results to be available before the PET. For these patients, it is recommended that the MRI appointment and lumbar puncture 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 performed and evaluated before the end of the screening period. In rare cases in which MRI needs to be repeated or any other unexpected delay owing 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 Patient Eligibility Checklist documenting the investigator's assessment of each screened patient with regard to the study's inclusion and exclusion criteria is to be completed by the investigator.

A screen failure log must be maintained by the investigator.

For patients who do not qualify for randomization, selected data will be retained and used by the Sponsor for the purpose of supporting APOE and CSF assay development and approval, and for patients in the WN28745-PET substudy, for the purpose of establishing CSF and PET concordance (see the WN28745-PET substudy protocol).

4.6.2 Assessments at Baseline

In order to be randomized to receive double-blind treatment, patients must have no significant change in medical, psychiatric, or neurologic condition, or change in medication since screening (as agreed upon by the Sponsor/Medical Monitor when appropriate). The recommended order of assessments and rating scales to be performed at baseline is as follows:

Patient	Caregiver
ADAS-Cog13	CDR (caregiver input)
MMSE	ADCS-ADL
10- to 20-minute break (optional)	
QoL-AD	NPI
CDR (patient interview)	ZCI-AD
	Dependence Scale
10- to 20-minute break (optional)	
SymptomGuide™ Facilitated GAS (if applicable)	
C-SSRS[a]	RUD-Lite

ADAS-Cog13 = Alzheimer's Disease Activity Scale–Cognitive (subscale) 13; ADCS-ADL = Alzheimer's Disease Cooperative Study–Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; GAS = Goal Attainment Scale; MMSE = Mini Mental State Examination; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease; NPI = Neuropsychiatric Inventory; QoL-AD = Quality of Life Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia.

[a] Study drug will be administered to patients following completion of the C-SSRS.

Vital signs, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples are recommended to be collected following scale assessments.

After all assessments indicated above have been completed, gantenerumab or matching placebo will be administered to patients subcutaneously at room temperature. Patients

should be observed for a minimum of 2 hours after dosing for the first four drug administrations, and then for a minimum of 1 hour after all remaining doses.

4.6.3 Assessments during Part 1

Patients will receive up to 26 SC administrations of study drug over the course of 100 weeks, with a 4-week interval between each dose. The final on-treatment efficacy and safety assessments are scheduled at Week 104, 4 weeks following the last dose.

The same schedule as above for baseline should be followed (omitting those that are not conducted per the schedule of assessments; see Appendix 1).

On each dosing day, after all assessments indicated in the schedule of assessments to be conducted prior to dosing have been completed, gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, patients should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses. For Doses 5 and beyond, the patient should be observed for a minimum of 1 hour. Patients should only leave the study center after injections if he or she appears to be tolerating the injections. When doses are to be administered remotely from the clinical sites, this may be done only by qualified health care providers as defined by local regulations who must remain with the patients for a minimum of 1 hour after each injection and be equipped with an adrenaline pen.

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. Patients and their caregivers 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.

Visits at which the patient receives study drug may take place within ± 7 days of the protocol-specified date as per the schedule of assessments in Appendix 1. However, all visits should be scheduled as close as possible to the exact day. It is preferred that all assessments for a visit be performed on the same day, but if necessary, assessments may be done over more than 1 day. Preferably, all clinical scales and assessments should be performed on the same day. Study drug administration should be performed only after all assessments/rating scales for the patient have been completed.

For sites and patients for whom this is practical, visits that require only dosing, vital sign measurements, urine pregnancy test, C-SSRS assessment, and adverse event assessment may be done at an alternate location conducted by appropriate health care professionals.

Please see Appendix 1 for the schedule of assessments during the treatment period.

4.6.3.1 Assessments during Open-Label Extension

Patients will receive SC administrations of open-label gantenerumab q4w. The follow-up visits are scheduled 4 and 16 weeks following the last dose *(follow-up visit at 16 weeks is not required for patients who enroll in Study WN41874)*.

The recommended order of assessments is as follows: ADAS-Cog, MMSE, CDR, followed by the safety assessments for patients, and CDR followed by ADCS-ADL for caregivers. After all assessments are completed, gantenerumab will be administered subcutaneously at room temperature. Patients who have received four doses or less of gantenerumab should be observed for a minimum of 2 hours after dosing. Patients who have received five or more doses of gantenerumab should be observed for a minimum of 1 hour after dosing.

4.6.3.2 Procedures for New MRI Findings

In addition to any local reading as per local procedures and requirements, all MRI scans 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. The Sponsor in turn may notify the MRI review committee (see Section 3.1.5).

Please refer to Section 5.1.4 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.3.3 Assessments at Study Completion/ Follow-Up Visit*s*

Patients who complete the double-blind treatment period (defined as completing 100 weeks of study drug treatment) should enter the final efficacy and safety assessment period 4 weeks following the last dose (Week 104), and subsequent 16- and 52-week follow-up periods (Weeks 116 and 152, respectively).

In addition, patients who complete the OLE will *undergo safety and limited efficacy assessments 4 weeks after the final dose (Follow-Up 1). Patients who do not enroll in Study WN41874 will undergo additional safety and limited efficacy assessments 16 weeks after the final dose (Follow-Up 2)*.

All patients who withdraw from treatment (whether double blind or open label), or discontinue from the study early will be asked to return for collection of safety and limited efficacy data at 4 and 16 weeks from the time of their last dose of study drug.

Autopsy reports, including cause of death, *should be requested* for all patients who die during the study (i.e., prior to the Week 52 follow-up visit *for patients in Part 1 and prior to the Follow-Up 1 or Follow-Up 2 visit, as applicable, for patients in Part 2*).

Please see the schedule of assessments to be performed at the study completion/early termination visit in Appendix 1 and Appendix 2.

4.6.3.4 Follow-Up Assessments

Patients will be asked to return to the clinic 4 and 16 weeks after the last dose of study drug for follow-up visits *(follow-up visit at 16 weeks is not required for patients who enroll in Study WN41874).*

When patients complete the treatment period or discontinue early, every effort should be made to ensure that the safety follow-up period and all related assessments are completed.

After the study completion/early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.6. Please see the schedule of follow-up assessments to be performed in Appendix 1 and Appendix 2.

4.6.3.5 Assessments at Unscheduled Visits

Assessments at unscheduled visits should be determined by the investigator based on clinical relevance and appropriateness to the cause of the unscheduled visit. The schedule of assessments in Appendix 1 allows for all assessments at the unscheduled visits.

4.7 PATIENT, TREATMENT, STUDY, AND SITE DISCONTINUATION

4.7.1 Patient Discontinuation

The investigator has the right to discontinue a patient from study drug or withdraw a patient from the study at any time. In addition, patients have the right to voluntarily discontinue study drug or withdraw from the study at any time for any reason. Reasons for discontinuation of study drug or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Any medical condition that the investigator or Sponsor determines may jeopardize the patient's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the patient
- Patient non-compliance with the study and/or study procedures, specifically defined in Part 1 as missing more than three consecutive dose administrations due to non-safety reasons or more than six visits in a calendar year.

Patients should be informed of circumstances under which their participation may be terminated by the investigator without the patient's consent. Any administrative or other reasons for withdrawal must be explained to the patient.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the

appropriate eCRF. However, patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.7.2 Discontinuation from Study Drug

Patients must discontinue study drug if they experience any of the following:

- Pregnancy
- Upon development of more than eight ARIA-H cumulatively for patients on the 225 mg or 300 mg doses
- Upon evidence of more than 10 ARIA-H, cumulatively

All patients who withdraw or discontinue from the study drug early will be requested to return for collection of safety and limited efficacy data at 4, 16, and 52 weeks from the time of their last dose of study drug *during Part 1 and at 4 and 16 weeks from the time of their last dose during Part 2.*

The primary reason for premature study drug discontinuation should be documented on the appropriate eCRF. Patients who discontinue study drug prematurely will not be replaced.

4.7.2.1 Withdrawal from Study

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. Patients will not be followed for any reason after consent has been withdrawn. Patients who withdraw from the study will not be replaced.

4.7.3 Study and Site Discontinuation

The Sponsor has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.
- Futility analyses from this or other studies with gantenerumab suggest that treatment with gantenerumab is likely not effective.
- Sponsor determines it is in the best interest of the patients.

The Sponsor will notify the investigator if the study is placed on hold, or if the Sponsor decides to discontinue the study or development program.

The Sponsor has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment
- Poor protocol adherence

- Inaccurate or incomplete data recording
- Non-compliance with the International Conference on Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all patients have completed and all obligations have been fulfilled)

5. ASSESSMENT OF SAFETY

5.1 SAFETY PLAN

Gantenerumab is not yet approved, and clinical development is ongoing. The safety plan for patients in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are ARIAs and injection-site reactions. Refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

5.1.1 Amyloid-Related Imaging Abnormalities

ARIA-E events were dose-, time-, and ApoE4-dependent, and well-managed through MRI monitoring and dose intervention algorithms. The vast majority of patients with ARIA-E reported no symptoms, and the ARIA-E resolved spontaneously when study drug was withheld. 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.

ARIA-H events were dose- and ApoE4-dependent and all events (in patients without ARIA-E) were asymptomatic. ARIA-H is managed through MRI monitoring and dose intervention algorithms.

All clinical trials with gantenerumab include APOE ε4 genotyping, MRI monitoring and an ARIA-based dose intervention algorithm. In case of clinical symptoms, the use of IV glucorticosteroids may be considered.

5.1.2 Injection-Site Reactions

Gantenerumab is generally well tolerated by patients. The local tolerability at injection sites was considered good, with minimal pain reported and occasionally with some mild erythema or inflammation. Injection-site reactions have been observed in up to one-third of healthy volunteers after SC administration. It is likely that the injection-site reactions are related to the injection volume. The events were mostly transient and mild in intensity.

Detailed information on the characteristic signs and symptoms of injection-site reactions (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page.

5.1.3 *Immunogenicity*

As with administration of any exogenous protein, a potential exists for the development of ADAs, which can be neutralizing and/or sensitizing, with the potential for producing febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low, given that it is a fully human antibody. There are no clinical findings indicative of an immunogenic response to gantenerumab. Patients should be informed about the signs and symptoms of hypersensitivity reactions and should be monitored for such reactions.

5.1.4 Management of Selected Adverse Events

5.1.4.1 Dosing Strategy and ARIA-Related Dose Adjustments in Part 1

All patients randomized to gantenerumab will receive a dose of 105 mg q4w for the first 24 weeks and, if eligible, the dose will be up-titrated to 225 mg q4w for the remainder of the study regardless of APOE ε4 status. Patients will undergo brain MRI examinations for ARIA-related safety monitoring as specified in the schedule of assessments. MRI after the Week 24 dose will determine eligibility for dose titration starting with the Week 28 dose. Patients will be eligible to receive 225 mg q4w starting with Week 28 if no ARIA-E and no more than one new microbleed are detected on any MRI scan up to and including the post-Week 24 MRI. In addition, the following dose adjustment and discontinuation rules for MRI safety-related findings will apply:

- At any time during the study upon emergence of single ARIA-E >2 cm or multiple ARIA-E, study drug will be withheld until the ARIA-E has resolved or significantly decreased and stabilized. Dosing can then be restarted with 105 mg q4w. If ARIA-E recurs (e.g., initial lesion increases in size, new lesion is detected in a different location), the patient will be discontinued from treatment (irrespective of the size of ARIA-E).
- A single ARIA-E finding of ≤ 2 cm does not require any dose change. Upon detection of such an ARIA-E finding, monthly MRI monitoring will be performed until the event has resolved.
- For patients on the 225 mg dose of gantenerumab who develop two new microbleeds on a single scan or three or four new microbleeds cumulatively the dose will be reduced to 105 mg. All patients who develop five or more new microbleeds cumulatively will be discontinued from study treatment.
- In case of both ARIA-E and ARIA-H, the most conservative approach should be followed.
- In case of ARIA findings, a PK sample will be obtained as soon as is practical once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H (e.g., unscheduled visit).

The iDMC will continue reviewing the incidence of ARIA and may recommend adjustment of the dosing regimen for the overall study population or in a specific APOE ε4 genotype.

5.1.4.2 Dosing Strategy and ARIA-Related Dose Adjustments in Part 2

Patients participating in Part 2 will undergo brain MRI examinations for ARIA-related safety monitoring prior to every dose increase (i.e., within 20 days after the end of a dose level). This MRI will determine eligibility for the next up-titration dose. Patients will be eligible for up-titration if no significant ARIA-E (i.e., no symptomatic ARIA or no ARIA with Barkhof Grand Total Score [BGTS] > 1) and no more than eight ARIA-H cumulatively are detected on any MRI scan.

In addition, the following dose adjustment and discontinuation rules for MRI safety-related findings will apply:

- In case of asymptomatic ARIA-E > 1 and < 4 BGTS: Continue study drug at the same dose level (i.e., do not up-titrate) and repeat MRI 4 weeks later:

  If ARIA-E is stable or has decreased, continue study drug at the same dose level and continue monthly MRI monitoring until event resolves. If ARIA-E resolves (i.e., BGTS = 0 or 1), resume up-titration as per Schedule of Assessments.

  If ARIA-E increases (BGTS ≥ 4) or symptoms develop, refer to the rule below.
- In case of symptomatic ARIA-E (any size) or asymptomatic ARIA-E with ≥ 4 BGTS: Temporarily interrupt study drug and implement monthly MRI monitoring until event resolves. Once symptoms and ARIA-E resolve (BGTS = 0 or 1), reintroduce study drug at the same dose given at the time the event was detected, and perform an MRI after 2 months of dosing. If no new ARIA-E is detected, resume up-titration and MRI monitoring as per Schedule of Assessments.
- In case of any new onset of ARIA-E: Treat in the same procedure as the first event (based on symptoms and BGTS).
- Patients who develop > 8 ARIA-H cumulatively will have their titration regimen suspended (i.e., no further up-titration) if they are receiving the 450 mg dose or higher. Patients who are on 225 mg or 300 mg dose and who develop more than eight ARIA-H will be discontinued from the study drug. At any dose, patients who develop > 10 ARIA-H cumulatively will be discontinued from the study drug.
- In case of both ARIA-E and ARIA-H, the most conservative approach should be followed.
- In case of ARIA findings, a PK sample will be obtained once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H (e.g., unscheduled visit).
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring due to ARIA findings should be conducted at approximately monthly intervals

The iDMC will continue to review the incidence of ARIA along with other safety findings until the majority of patients have reached the target dose and may recommend

adjustment of the dosing regimen for the overall study population or in a specific APOE ε 4 genotype. In addition, significant ARIA findings will be submitted to an iMRI-C (as defined in iMRI-committee charter).

5.2 SAFETY PARAMETERS AND DEFINITIONS

Safety assessments will consist of monitoring and recording adverse events, including serious adverse events and adverse events of special interest, performing protocol-specified safety laboratory assessments, measuring protocol-specified vital signs, and conducting other protocol-specified tests that are deemed critical to the safety evaluation of the study.

Certain types of events require immediate reporting to the Sponsor, as outlined in Section 5.4.

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event 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 product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition), except as described in Section 5.3.5.10
- 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)

5.2.2 Serious Adverse Events (Immediately Reportable to the Sponsor)

A serious adverse event is any adverse event that meets any of the following criteria:

- Fatal (i.e., the adverse event actually causes or leads to death)
- Life threatening (i.e., the adverse event, in the view of the investigator, places the patient at immediate risk of death)

  This does not include any adverse event that had it occurred in a more severe form or was allowed to continue might have caused death.

- Requires or prolongs inpatient hospitalization (see Section 5.3.5.11)
- 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)
- Congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Significant medical event in the investigator's judgment (e.g., may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The terms "severe" and "serious" are not synonymous. Severity refers to the intensity of an adverse event (rated as mild, moderate, or severe, see Section 5.3.3); 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.

Serious adverse events 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 5.4.2 for reporting instructions).

5.2.3 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 5.4.2 for reporting instructions). Adverse events of special interest for this study include the following:

- 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 5.3.5.7)
- 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 indicating an infection in a patient exposed to a medicinal product. This term only applies when a contamination of the study drug is suspected.

5.2.4 Selected Adverse Events

To further elucidate potential clinical implications of ARIA findings, patients will be contacted up to 1 week before each MRI is performed and asked if they have experienced CNS adverse events. The eliciting of these adverse events should be

according to Section 5.3.2. 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 the following selected adverse events:

- ARIA-E: ARIAs suggestive of vasogenic edema and sulcal effusions
- ARIA-H: ARIAs suggestive of microhemorrhages and hemosiderin deposits

5.3 METHODS AND TIMING FOR CAPTURING AND ASSESSING SAFETY PARAMETERS

The investigator is responsible for ensuring that all adverse events (see Section 5.2.1 for definition) are recorded on the Adverse Event eCRF and reported to the Sponsor in accordance with instructions provided in this section and in Sections 5.4–5.6.

For each adverse event recorded on the Adverse Event eCRF, the investigator will make an assessment of seriousness (see Section 5.2.2 for seriousness criteria), severity (see Section 5.3.3), and causality (see Section 5.3.4).

5.3.1 Adverse Event Reporting Period

Investigators or their designees will seek information on adverse events at each patient contact. All adverse events, whether reported by the patient or noted by study personnel, will be recorded in the patient's medical record and on the Adverse Event eCRF.

After informed consent has been obtained **but prior to initiation of study drug**, only serious adverse events caused by a protocol-mandated intervention (e.g., invasive procedures such as biopsies, discontinuation of medications) should be reported (see Section 5.4.2 for instructions for reporting serious adverse events).

After initiation of study drug, all adverse events, regardless of relationship to study drug, will be reported until 52 weeks after the last dose *of study drug during Part 1 and until 4 or 16 weeks, as applicable, after the last dose of study drug during Part 2*. After this period, the investigator should report any serious adverse events that are believed to be related to study drug treatment (see Section 5.6).

5.3.2 Eliciting Adverse Event Information

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?"

5.3.3 Assessment of Severity of Adverse Events

Table 4 provides guidance for assessing adverse event severity.

Table 4 Adverse Event Severity Grading Scale

Severity	Description
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 5.2.2).

5.3.4 Assessment of Causality of Adverse Events

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. The following guidance should be taken into consideration:

- 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

For patients receiving approved AD treatments, causality will be assessed individually for each protocol-mandated therapy.

5.3.5 Procedures for Recording Adverse Events

Investigators or their designees should use correct medical terminology/concepts when recording adverse events on the Adverse Event eCRF. Avoid colloquialisms and abbreviations.

Only one adverse event term should be recorded in the event field on the Adverse Event eCRF.

5.3.5.1 Injection Reaction

Individual signs and symptoms of injection-site reactions (e.g., erythema, pain) should be reported on the 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.

5.3.5.2 Diagnosis versus Signs and Symptoms

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. If a 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.

5.3.5.3 Adverse Events Occurring Secondary to Other Events

In general, adverse events occurring 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. However, medically significant adverse events occurring secondary to an initiating event that are separated in time should be recorded as independent events 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 subsequent 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.

5.3.5.4 Persistent or Recurrent Adverse Events

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 5.4.2 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.

5.3.5.5 Abnormal Laboratory Values

Not every laboratory abnormality qualifies as an adverse event. A laboratory test 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., dose modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Clinically significant in the investigator's judgment

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× the ULN associated with cholecystitis), only the diagnosis (i.e., cholecystitis) 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 if 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."

Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

If a patient develops moderate to severe neutropenia (absolute neutrophil count $< 1000/mm^3$) 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 should be done only after the investigator discusses the case with the Sponsor's Medical Monitor.

5.3.5.6 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., dose 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 not be repeatedly recorded on the Adverse Event eCRF, unless the etiology changes. The initial severity of the event should be recorded, and the severity or seriousness should be updated any time the event worsens.

5.3.5.7 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($> 3\times$ the upper limit of normal [ULN]) in combination with either an elevated total bilirubin ($> 2\times$ the ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury. Therefore, investigators must report as an adverse event the occurrence of either of the following:

- Treatment-emergent ALT or AST $> 3\times$ ULN in combination with total bilirubin $> 2\times$ ULN
- Treatment-emergent ALT or AST $> 3\times$ ULN in combination with clinical jaundice

The most appropriate diagnosis or (if a diagnosis cannot be established) the abnormal laboratory values should be recorded on the Adverse Event eCRF (see Section 5.3.5.2) and reported to the Sponsor immediately (i.e., no more than 24 hours after learning of the event), either as a serious adverse event or an adverse event of special interest (see Section 5.4.2).

5.3.5.8 Deaths

All deaths that occur during the protocol-specified adverse event reporting period (see Section 5.3.1), regardless of relationship to study drug, must be recorded on the Adverse Event eCRF and immediately reported to the Sponsor (see Section 5.4.2). 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 due to presumed cardiac causes (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.

5.3.5.9 Preexisting Medical Conditions

A preexisting medical condition is one that is present at the screening visit for this study. Such conditions should be recorded on the General Medical History and Baseline Conditions eCRF.

A preexisting medical condition should be recorded as an adverse event only if the frequency, severity, or character of the condition worsens during the study. When recording such events on the Adverse Event eCRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

5.3.5.10 Lack of Efficacy or Worsening of Alzheimer's Disease

Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events. These data will be captured as efficacy assessment data only. In most cases, the expected pattern of progression will be based on symptomatic deterioration. However, every effort should be made to document progression using objective criteria. If there is any uncertainty as to whether an event is due to disease progression, it should be reported as an adverse event.

5.3.5.11 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in Section 5.2.2), 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
- Planned hospitalization required by the protocol (e.g., for study drug administration or insertion of access device for study drug administration)
- Hospitalization for a preexisting condition, provided that both of the following criteria are 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 the disease.

  The patient has not suffered an adverse event.

An event that leads to hospitalization under the following circumstances is not considered to be a serious adverse event, but should be reported as an adverse event instead:

- Hospitalization that was necessary because of patient requirement for outpatient care outside of normal outpatient clinic operating hours

5.3.5.12 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 5.4.2).

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

5.3.5.13 Patient- and Caregiver-Reported Outcome Data

Adverse event reports will not be derived from patient- or caregiver-reported outcome data. However, if any patient's or caregiver's responses suggestive of a possible adverse event are identified during site review of the patient- or caregiver-reported outcome questionnaires, site staff will alert the investigator, who will determine if the criteria for an adverse event have been met and will document the outcome of this assessment in the patient's medical record per site practice. If the event meets the criteria for an adverse event, it will be reported on the Adverse Event eCRF.

5.4 IMMEDIATE REPORTING REQUIREMENTS FROM INVESTIGATOR TO SPONSOR

Certain events require immediate reporting to allow the Sponsor to take appropriate measures to address potential new risks in a clinical trial. The investigator must report such events to the Sponsor immediately; under no circumstances should reporting take place more than 24 hours after the investigator learns of the event. The following is a list of events that the investigator must report to the Sponsor within 24 hours after learning of the event, regardless of relationship to study drug:

- Serious adverse events
- Adverse events of special interest
- Pregnancies

The investigator must report new significant follow-up information for these events to the Sponsor immediately (i.e., no more than 24 hours after becoming aware of the information). New significant information includes the following:

- New signs or symptoms or a change in the diagnosis
- Significant new diagnostic test results
- Change in causality based on new information
- Change in the event's outcome, including recovery
- Additional narrative information on the clinical course of the event

Investigators must also comply with local requirements for reporting serious adverse events to the local health authority and IRB/EC.

5.4.1 Emergency Medical Contacts

Medical Monitor (Roche Medical Responsible) Contact Information

Primary Contact

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

Secondary Contact

Medical Monitor: [redacted], M.D.

Mobile Telephone No.: [redacted]

To ensure the safety of study patients, 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 a Roche Medical Monitor, and track all calls. The Emergency Medical Call Center Help Desk will be available 24 hours per day, 7 days per week. Toll-free numbers for the Help Desk and Medical Monitor contact information will be distributed to all investigators (see "Protocol Administrative and Contact Information & List of Investigators").

5.4.2 Reporting Requirements for Serious Adverse Events and Adverse Events of Special Interest

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), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Patients

Female patients of childbearing potential will be instructed to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the last dose of study drug. A Pregnancy Report eCRF should be completed by the investigator immediately (i.e., no more than 24 hours after learning of the pregnancy) and submitted via the EDC system. A pregnancy report will automatically be generated and sent to Roche Safety Risk Management. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the patient, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the patient should continue until conclusion of the pregnancy. Any serious adverse events associated with the pregnancy (e.g., an event in the fetus, an event in the mother during or after the pregnancy, or a congenital anomaly/birth defect in the child) should be reported on the Adverse Event eCRF.

In the event that the EDC system is unavailable, a Clinical Trial Pregnancy 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 pregnancy), using the fax numbers provided to investigators (see "Protocol Administrative and Contact Information & List of Investigators"). Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

5.4.3.2 Abortions

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; see Section 5.4.2).

5.4.3.3 Congenital Anomalies/Birth Defects

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; see Section 5.4.2).

5.4.4 Reporting Requirements for Medical Device Complaints

Gantenerumab is provided as a G3-derived high-concentration liquid formulation either in a prefilled syringe with a needle safety device or in a vial. The investigator must report all medical device complaints to the Sponsor. The investigator must document as much information as possible on the Medical Device Complaint Form (PD103), including the product batch number, type of product, and expiration date. GCP-related complaints or deviations that might impact subject's safety should be forwarded to the scientific responsible for assessment of impact and determination of follow-up actions if needed. If the complaint results in an adverse event (non-serious or serious), the adverse event must be reported on the Adverse Event eCRF as per Section 7.2. If the event is serious, the Adverse Event eCRF must be completed and submitted through the EDC system immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PATIENTS AFTER ADVERSE EVENTS

5.5.1 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. If, after follow-up, return to baseline status or stabilization cannot be established, an explanation should be recorded on the Adverse Event eCRF.

All pregnancies reported during the study should be followed until pregnancy outcome. If the EDC system is not available at the time of pregnancy outcome, follow reporting instructions provided in Section 5.4.3.1.

5.5.2 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, electronic mail, 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.

5.6 POST-STUDY ADVERSE EVENTS

At the time of study completion or study discontinuation, the investigator should instruct each patient to report to the investigator any subsequent *serious* adverse events that the patient's personal physician believes could be related to prior study drug treatment or study procedures.

The investigator is not required to actively monitor patients for adverse events after the end of the adverse event reporting period (defined as 52 weeks after the last dose of study drug *during Part 1 and 4 or 16 weeks, as applicable, after the last dose of study drug during Part 2*. However, the Sponsor should be notified if the investigator becomes aware of any serious adverse event that occurs after the end of the adverse event reporting period (defined as 52 weeks after the last dose of study drug *during Part 1 and 4 or 16 weeks, as applicable, after the last dose of study drug during Part 2)*, if the event is believed to be related to prior study drug treatment.

The investigator should report these events directly to Roche Safety Risk Management by telephone or by fax machine using the Serious Adverse Event Reporting Form and fax cover sheet (see "Protocol Administrative and Contact Information & List of Investigators").

5.7 EXPEDITED REPORTING TO HEALTH AUTHORITIES, INVESTIGATORS, INSTITUTIONAL REVIEW BOARDS, AND ETHICS COMMITTEES

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 *events through use of the reference safety information in the following documents (see Table 5).*

Table 5 Documents to Be Used for Reference Safety Information

Drug	*Document*
Gantenerumab	*Gantenerumab Investigator's Brochure*
Florbetapir [^{18}F] (Study WN28745 Amyloid PET Substudies)	*Florbetapir [^{18}F] Investigator's Brochure*
[^{18}F] RO6958948 (Study WN28745 Tau PET Substudy)	*[^{18}F] RO6958948 Investigator's Brochure*

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 *applicable reference document*.

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

6. STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN

6.1 STATISTICAL CONSIDERATIONS AND ANALYSIS PLAN IN PART 1

6.1.1 Determination of Sample Size

The purpose of this study was to test the treatment effect of gantenerumab relative to placebo. Point and interval estimates of the true treatment difference were to be presented.

A target sample size of 500 patients per arm was to be enrolled into the study. With this sample size, and based on the assumptions listed below, the study was estimated to have at least 80% power at a two-sided α level of 0.05 for testing the hypotheses of each of the co-primary efficacy endpoints using the MMRM analysis.

- Expected difference between treatment arms in the absolute change from baseline at Week 104 in ADAS-Cog13 of approximately 2.3 points, with a SD of 10.4
- Expected difference between treatment arms in the absolute change from baseline at Week 104 in ADCS-ADL of approximately 2.5 points, with a SD of 10.9
- Expected withdrawal rate (including censoring from the efficacy analysis owing to changes in medications) of approximately 30%

The SD values used for these calculations (10.4 for ADAS-Cog13 and 10.9 for ADCS-ADL) were estimated on the basis of publicly available results for the change from baseline in these endpoints from the mild subgroups of the bapineuzumab and solanezumab Phase III studies. Based on these results, estimates of 9.0 and 9.5 were derived for the standard deviations of these endpoints respectively at Month 18. Each of these values was increased by approximately 15% to reflect an anticipated increase in variability over time (because of the 24-month treatment duration of this study), which results in SD estimates of 10.4 and 10.9.

Also, on the basis of recently published data from the bapineuzumab and solanezumab Phase III studies as well as the patient-level data available from ADNI, the mean baseline ADAS-Cog13 values was expected to be approximately 30 points, and the mean baseline ADCS-ADL values was expected to be approximately 57 points. The change from baseline in the placebo group at 24 months is estimated to be approximately 10.0 points for ADAS-Cog13 and approximately 10.5 points for ADCS-ADL.

The mean placebo-adjusted change from baseline (2.4 for ADAS-Cog13 and 2.5 for ADCS-ADL) and SD values used for these calculations, therefore, each correspond to a standardized effect of approximately 0.24, which is expected to represent a clinically relevant treatment difference for these endpoints.

6.1.2 Summaries of Conduct of Study

Descriptive statistics were to be used to summarize study conduct measures, such as study disposition (including premature withdrawals from treatment), incidence of protocol deviations, percentage of intended dose administered, and incidence of incorrect treatment allocation.

6.1.3 Summaries of Treatment Group Comparability

Descriptive statistics were to be used to assess differences between the treatment arms in baseline levels of the primary and key secondary efficacy measures for the intent-to-treat (ITT) population. For all analyses, the baseline observation was defined as the last observation with a non-missing value taken prior to the start of double-blind treatment. Efficacy Analyses.

The primary analysis population for all efficacy analyses was the ITT analysis population. The ITT population would have included all randomized patients who receive at least one dose of study drug, with patients grouped according to the treatment assigned at randomization.

6.1.3.1 Primary Efficacy Endpoint

The co-primary efficacy endpoints were the absolute change from baseline to the end of Week 104 in ADAS-Cog13 and ADCS-ADL.

For each of the primary endpoints, the null and alternative hypotheses to be tested were:

$$H_0: \mu = 0 \text{ versus } H_A: \mu \neq 0$$

for which μ is the assumed treatment difference in the absolute change from baseline in the endpoint between the gantenerumab and placebo groups. For each endpoint, the null hypothesis of no treatment difference will be rejected if the two-sided p-value is ≤ 0.05.

The primary efficacy analyses were to include all randomized patients, with patients grouped according to the treatment assigned at randomization.

For the assessment of difference between the gantenerumab group and placebo with regard to the mean change from baseline in each primary endpoint at the end of Week 104, an MMRM analysis, incorporating data up to 104 weeks of treatment, was to be used to utilize all the data collected over time. For the primary efficacy analyses, all observations recorded after any modification of the patient's baseline AD medication

regimen (change in the dose of the medication or initiation of a new medication) were to be excluded.

For each co-primary endpoint, the model would have included the absolute change from baseline in the endpoint as the dependent variable. The effects in the model would have included independent variables of treatment, assessment weeks relative to the first dose of study medication (i.e., time), treatment-by-time interaction, APOE ε4 status (carrier versus non-carrier), baseline AD treatment (either receiving AD treatment or not), and the respective baseline value as a covariate. An unstructured variance-covariance structure was to be applied to model the within-patient errors and to enable the inclusion of data from patients with incomplete data across scheduled timepoints.

In order to assess the effect of missing data on the analysis results for the co-primary and key secondary endpoints, sensitivity analyses were to be performed using multiple imputation methods and pattern mixture models. Sensitivity analyses were also to be performed in which observations recorded after any modification of a patient's baseline AD medication regimen would be included.

Additional details will be documented in the Statistical Analysis Plan.

6.1.3.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 3.5.2 (including cognitive endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) was to be analyzed using an MMRM analysis model as described above for the primary efficacy endpoint.

The time to first occurrence of the key secondary endpoint of time to clinical decline was to be analyzed using a stratified proportional hazards model, with APOE ε4 genotype as a stratification factor.

A responder analysis for absolute change from baseline in ADAS-Cog13 at Week 104 was to be performed using a Cochran-Mantel-Haenszel test, with APOE ε4 genotype as a stratification factor. In this analysis, patients who did not have an assessment at Week 104, or who had a modification in the baseline AD medication regimen prior to the Week 104 assessment, were to be considered as non-responders.

6.1.3.3 Testing Hierarchy

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the co-primary endpoints and the key secondary endpoints into the analysis, the hierarchical testing procedure in the protocol was specified as follows.

Step 1a: Test the change from baseline in ADAS-Cog (a co-primary efficacy endpoint) comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

Step 1b: Test the change from baseline in ADCS-ADL (a co-primary efficacy endpoint) comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

The result of Step 1 of the testing procedure is considered statistically significant only if the p-values for both Steps 1a and 1b (i.e., both co-primary efficacy endpoints) are statistically significant at $\alpha = 0.05$. If either p-value is > 0.05, the result of Step 1 is considered non-significant and no further testing will be performed.

If Step 1a **and** Step 1b are significant, continue testing.

↓

Step 2: Test the time to first occurrence of clinical decline between the gantenerumab and placebo arms at $\alpha = 0.05$.

If Step 2 is significant,

↓

Step 3: Test the change from baseline in CDR-SB comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

If Step 3 is significant,

↓

Step 4: Test in ADAS-Cog responder comparison between the gantenerumab and placebo arms at $\alpha = 0.05$.

6.1.4 Safety Analyses

The safety analysis population will include all randomized patients who received at least one dose of study drug, with patients grouped according to the treatment actually received.

The following safety outcome measures will be summarized using descriptive statistics:

- Incidence and nature of MRI safety findings: ARIA-E and ARIA-H
- Incidence, nature, and severity of serious adverse events

- Incidence, nature, and severity of adverse events

  Adverse events will be summarized by preferred term.
- Incidence of treatment discontinuations because of adverse events
- Mean changes in clinical laboratory tests from baseline over time and incidence of treatment-emergent abnormal laboratory values.
- Mean changes in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Incidence of anti-gantenerumab antibodies
- Physical and neurologic examination abnormalities
- Mean changes in vital signs assessment from baseline over time and incidence of abnormal vital sign measurements
- Changes in C-SSRS scores from baseline over time

6.1.5 Pharmacokinetic Analyses

Non-linear 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 PK model. The selection of parameters and the derivation of individual measures of exposure, such as $AUC_{0-\tau}$, C_{max}, and C_{trough}, will depend on the final PK model used for this analysis. All PK parameters will be presented by listings and descriptive summary statistics, including the arithmetic mean (for $AUC_{0-\tau}$, C_{max}, and C_{trough}), median, range, SD, and CV. Details of the mixed-effects modeling analysis will be described in the Modeling and Simulation Analysis Plan and results of this analysis will be reported separately. The influence of background medication on the pharmacokinetics of gantenerumab will be explored and, if appropriate, concentration–effect relationships may be assessed post hoc for PD, efficacy, or safety measures.

6.1.6 Exploratory Analyses

An analysis will be performed to explore association of the treatment effect with patient genotypes to assess the influence of the APOE ε4 status and Fcγ receptor genotypes on the gantenerumab treatment effect, the primary efficacy variable, and selected safety parameters and summarized by each of the genotypes. Inferential statistics may be applied in case the difference is clinically relevant.

6.1.7 Subgroup Analyses

Since this is a global study, the effect of some demographic variables and baseline characteristic such as race and region on efficacy and safety will be summarized within subgroups using descriptive statistics (please see subgroups below). Additional exploratory analyses of efficacy results may be performed using an MMRM model, with the subgroup, a treatment-by-subgroup interaction term, and a subgroup-by-time interaction terms included along the independent effects described above. This

exploratory subgroup analysis may be important in understanding the effect of these variables on efficacy and safety. 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 ε4 status
- Fcγ receptor genotype
- Region

Additional subgroup analyses may be performed with subgroups defined based on baseline levels of CSF t-tau, p-tau, t-tau to Aβ1–42 ratio, and p-tau to Aβ1–42 ratio.

Since Part 1 (i.e., the double-blind period) has been suspended and replaced by an OLE, the primary and key secondary efficacy analyses will not be performed. However, exploratory and descriptive analyses will be conducted at the end of Part 1.

6.2 ANALYSES IN PART 2

As Part 2 is an OLE, regular safety analyses will be conducted as described in Section 6.1.4. In addition, descriptive statistics and changes from baseline will be used to explore clinical findings (including efficacy, global functioning, and biomarkers). PK analysis will be conducted according to Section 6.1.5.

6.3 INTERIM ANALYSES

An interim analysis for futility was originally scheduled when approximately 50% of patients had completed 104 weeks of the double-blind treatment period. These results were to be reviewed by the IDMC. If the analysis of the primary endpoint results at the time of this interim analysis indicated that the predictive probability of success for the trial was $<10\%$ for either ADAS-Cog13 or ADCS-ADL, then the committee may recommend that the trial be terminated for futility. No adjustment for multiple comparisons was to be made to the α level for the analysis, as the decision rules for the futility analysis do not allow for the opportunity to stop the study early for overwhelming efficacy. This interim analysis was to be conducted by an independent Data Collection Center and will be reviewed by the iDMC.

There is no interim analysis scheduled for the OLE. However, the Sponsor will review the data on an ongoing basis.

7. DATA COLLECTION AND MANAGEMENT

7.1 DATA QUALITY ASSURANCE

The Sponsor will be responsible for data management of this study, including quality checking of the data. Data entered manually will be collected via EDC using eCRFs. Sites will be responsible for data entry into the EDC system. In the event of discrepant data, the Sponsor will request data clarification from the sites, which the sites will resolve electronically in the EDC system.

The Sponsor will produce an EDC Study Specification document that describes the quality checking to be performed on the data. All electronic data from external vendors will be sent directly to the Sponsor, using the Sponsor's standard procedures to handle and process the electronic transfer of these data.

eCRFs and correction documentation will be maintained in the EDC system's audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

All rating scales data will be captured electronically. The symptom-guide facilitated goal-attainment scaling will be entered via a Web-based database. The other scales listed in Section 4.5.6.11 will be recorded directly into device laptop provided by a vendor. All other scales will be completed on paper and entered into the vendor-provided laptop by site staff. This device is designed for entry of data in a manner that is attributable, secure, and accurate in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The device data are available for view access only through secure access to an online Web portal. Only identified and trained users may view the data, and their actions become part of the audit trail. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

In the event that the device is not working, a paper backup for should be used to collect the rating scales data in Section 4.5.6.11. When the device becomes available, the data should then be entered into the device and recorded that paper backup was used.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed using a Sponsor-designated EDC system. Sites will receive training and have access to a manual for appropriate eCRF completion. eCRFs will be submitted electronically to the Sponsor and should be handled in accordance with instructions from the Sponsor.

All eCRFs should be completed by designated, trained site staff. eCRFs should be reviewed and electronically signed and dated by the investigator or a designee.

At the end of the study, the investigator will receive patient data for his or her site in a readable format on a compact disc that must be kept with the study records. Acknowledgement of receipt of the compact disc is required.

7.3 ELECTRONIC RATING SCALE DATA

Patients, caregivers, and appropriate site staff will use a laptop to record selected rating scales data, including clinician, patient and caregiver-reported data. The data will be transmitted via Web automatically after entry to a centralized database at the vendor. The data may be reviewed by site staff via secure access to an online Web portal.

Once the study is complete, the rating scales data, audit trail, and trial and system documentation will be archived. The investigator will receive patient data for the site in both human- and machine-readable formats on an archival-quality compact disc that must be kept with the study records as source data. Acknowledgement of receipt of the compact disc is required. In addition, the Sponsor will receive all patient data in a machine-readable format on a compact disc.

7.4 SOURCE DATA VERIFICATION

Study monitors will perform ongoing source data verification to confirm that critical protocol data (i.e., source data) entered by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented for the first time. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, PROs, evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, microfiche, photographic negatives, microfilm or magnetic media, X-rays, patient files, and records kept at pharmacies, laboratories, and medico-technical departments involved in a clinical trial.

Before study initiation, the types of source documents that are to be generated will be clearly defined in the Trial Monitoring Plan. This includes any protocol data to be entered directly onto the eCRFs and electronically administered rating scales per Section 7.5 (i.e., no prior written or electronic record of the data) and considered source data.

Source documents that are required to verify the validity and completeness of data entered onto the eCRFs must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 7.6.

To facilitate source data verification, the investigators and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related

monitoring, Sponsor audits, and IRB/EC review. The investigative site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into an investigative site's computerized medical record system (i.e., in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, the name of the person making the change, and date of the change.

7.6 RETENTION OF RECORDS

Records and documents pertaining to the conduct of this study and the distribution of IMP, including eCRFs, ePRO data (if applicable), Informed Consent Forms, laboratory test results, and study drug inventory records, must be retained by the Principal Investigator for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national or local health authorities, whichever is longer. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

8. ETHICAL CONSIDERATIONS

8.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the ICH E6 guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, or the laws and regulations of the country in which the research is conducted, whichever affords the greater protection to the individual. The study will comply with the requirements of the ICH E2A guideline (Clinical Safety Data Management: Definitions and Standards for Expedited Reporting). Studies conducted in the United States or under a U.S. Investigational New Drug (IND) Application will comply with U.S. FDA regulations and applicable local, state, and federal laws. Studies conducted in the EU/EEA will comply with the EU Clinical Trial Directive (2001/20/EC).

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form and ancillary sample Informed Consent Forms such as Caregiver's Informed Consent Form will be provided to each site. If applicable, it will be provided in a certified translation of the local language. The Sponsor or its designee must review and approve any proposed deviations from the

Sponsor's sample Informed Consent Forms or any alternate consent forms proposed by the site (collectively, the "Consent Forms") before IRB/EC submission. The final IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Informed Consent Form will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each patient the objectives of the exploratory research. Patients will be told that they are free to refuse to participate and may withdraw their specimens at any time and for any reason during the storage period. A separate, specific signature will be required to document a patient's agreement to allow any remaining specimens to be used for exploratory research. Patients who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the patient and/or the patient's LAR and the caregiver before his or her participation in the study. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to participation in the study. If the LAR co-signs the Consent Form with the patient, the patient will still need to provide assent in case he/she is no longer capable of providing consent. This will allow the LAR to make decisions on the patient's behalf. Assent implies willingness or, minimally, lack of objection to taking part and will need to be documented by the site.

The Consent Forms should be revised whenever there are changes to study procedures or when new information becomes available that may affect the willingness of the patient to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

If the Consent Forms are revised (through an amendment or an addendum) while a patient is participating in the study, the patient or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained using the updated/revised Consent Forms for continued participation in the study. If the LAR co-signs the Consent Form with the patient, the patient will still need to provide assent in case he/she is no longer capable of providing consent.

A copy of each signed Consent Form must be provided to the patient or the patient's legally authorized representative. All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include patient authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act (HIPAA) of 1996. If the site utilizes a separate Authorization Form for patient authorization for use and disclosure of personal health information under the HIPAA regulations, the review, approval, and other processes outlined above apply except that IRB review and approval may not be required per study site policies.

8.3 INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the IRB/EC by the Principal Investigator and reviewed and approved by the IRB/EC before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB/EC.

The Principal Investigator is responsible for providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC. Investigators are also responsible for promptly informing the IRB/EC of any protocol amendments (see Section 9.6).

In addition to the requirements for reporting all adverse events to the Sponsor, investigators must comply with requirements for reporting serious adverse events to the local health authority and IRB/EC. Investigators may receive written IND safety reports or other safety-related communications from the Sponsor. Investigators are responsible for ensuring that such reports are reviewed and processed in accordance with health authority requirements and the policies and procedures established by their IRB/EC, and archived in the site's study file.

8.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may only be disclosed to third parties as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of the national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRB/EC for each study site, as appropriate.

8.5 FINANCIAL DISCLOSURE

Investigators will provide the Sponsor with sufficient, accurate financial information in accordance with local regulations to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate health authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study (i.e., last patient, last follow-up visit).

9. STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

9.1 STUDY DOCUMENTATION

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including, but not limited, to the protocol, protocol amendments, Informed Consent Forms, and documentation of IRB/EC and governmental approval. In addition, at the end of the study, the investigator will receive the patient data, which includes an audit trail containing a complete record of all changes to data.

9.2 PROTOCOL DEVIATIONS

The investigator should document and explain any protocol deviations. The investigator should promptly report any deviations that might impact 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.

9.3 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, patient medical records, and eCRFs. The investigator will permit national and local health authorities, Sponsor monitors, representatives, and collaborators, and the IRBs/ECs to inspect facilities and records relevant to this study.

9.4 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in the Roche standard operating procedures.

This study will be sponsored by F. Hoffmann-La Roche Ltd. Roche will provide clinical operations oversight, site monitoring and management, data management support, and medical monitoring.

Drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, MRI, specified laboratory tests, pharmacokinetics, rating scales evaluation, and PET, if applicable). At select sites and specified visits, study drug administration and safety assessments may be performed by home nursing staff.

9.5 PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a trial, the Sponsor is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. For more information, refer to the Roche Global Policy on Sharing of Clinical Trials Data at the following Web site:

www.roche.com/roche_global_policy_on_sharing_of_clinical_study_information.pdf

The results of this study may be published or presented at scientific congresses. For all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to submit a journal manuscript reporting primary clinical trial results within 6 months after the availability of the respective clinical study report. In addition, for all clinical trials in patients involving an IMP for which a marketing authorization application has been filed or approved in any country, the Sponsor aims to publish results from analyses of additional endpoints and exploratory data that are clinically meaningful and statistically sound.

The investigator must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. 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, the Sponsor 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 (i.e., between the Sponsor and the coordinating investigator).

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

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

9.6 PROTOCOL AMENDMENTS

Any protocol amendments will be prepared by the Sponsor. Protocol amendments will be submitted to the IRB/EC and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the IRB/EC and regulatory authorities (as locally required) before implementation of any changes, except for changes necessary to eliminate an immediate hazard to patients or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

10. REFERENCES

Alzheimer's Association. 2015 Alzheimer's disease facts and figures. Available at: http://www.alz.org/facts/downloads/ff_quickfacts_2015.pdf. Accessed on 9 July 2015.

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders, 5th edition: DSM-5. Washington D.C.: 2013.

Bateman RJ, Benzinger TL, Berry S, et al. The DIAN-TU Next Generation Alzheimer's prevention trial: adaptive design and disease progression model. Alzheimer's Dementia 2017;13:8–19.

Becker RE, Greig NH. Alzheimer's disease drug development: old problems require new priorities. CNS Neurol Disord Drug Targets 2008;7:499–511.

Binnewijzend MAA, Schoonheim MM, Sanz-Arigita E, et al. Resting-state fMRI changes in Alzheimer's disease and mild cognitive impairment. Neurbiology Aging 2012;33:2018–28.

Blennow K, Hampel H, Weiner M, et al. Cerebrospinal fluid and plasma biomarkers in Alzheimer disease. Nat Rev Neurol 2010;6:131–44.

Brier MR, Thomas JB, Snyder AZ, et al. Loss of intranetwork and internetwork resting state functional connections with Alzheimer's disease progression. J Neurosci 2012;32:8890–9.

Cano SJ, Poser HB, Moline ML, et al. The ADAS-Cog in Alzheimer's disease clinical trials: psychometric evaluation of the sum of its parts. J Neurol Neurosurg Psychiatry 2010;81:1363–8.

Cummings JL. Defining and labeling disease-modifying treatments for Alzheimer's disease. Alzheimer Dement 2009;5:406–18.

Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. Neurology 1994;44:2308–14.

Delor I, Charoin JE, Gieschke R, et al. Modeling Alzheimer's Disease Progression Using Disease Onset Time and Disease Trajectory Concepts Applied to CDR-SOB Scores From ADNI. CPT Pharmcometrics Syst Pharmacol 2013;2:e78.

Doody RS. Phase 3 studies of solanezumab for mild to moderate Alzheimer Solanezumab Phase 3 Data Call, 8 October 2012, http://lilly.mediaroom.com/index.php?s=9042&item=134212.

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). Discussion paper on the clinical investigation of medicines for the treatment of Alzheimer´s disease and other dementias. 23 October 2014. Available from http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2014/10/WC500176827.pdf (Doc. Ref. EMA/CHMP/539931/2014 Corr).

European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP). Qualification opinion of Alzheimer's disease novel methodologies/biomarkers for the use of CSF Aβ 1-42 and t-tau and/or PET-amyloid imaging (positive/negative) as biomarkers for enrichment, for use in regulatory clinical trials in mild and moderate Alzheimer's disease. 16 February 2012 (EMA/CHMP/SAWP/893622/2011).

Filippi M, Agosta F. Structural and functional network connectivity breakdown in Alzheimer's disease studies with magnetic resonance imaging techniques. J Alzheimer's Dis 2011;24:455–74.

Fisk JD, Beattie BD, Donnelly M, et al. Disclosure of dementia diagnosis. Alzheimer's Dementia 2007;3:404–10.

Food and Drug Administration (FDA), U.S. Department of Health and Human Services, Center for Drug Evaluation and Research. Draft guidance for industry, Alzheimer's disease: developing drugs for the treatment of early stage disease. February 2013. Available from: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM338287.pdf. Accessed 20 September 2013.

Fox NC, Black RS, Gilman S, et al. Effects of Abeta immunization (AN1792) on MRI measures of cerebral volume in Alzheimer disease. Neurology 2005;64:1563–72.

Fox NC, Cousens S, Scahill R, et al. Using serial registered brain magnetic resonance imaging to measure disease progression in Alzheimer disease: power calculations and estimates of sample size to detect treatment effects. Arch Neurol 2000;57:339–44.

Fox NC, Kennedy J. Structural imaging markers for therapeutic trials in Alzheimer's disease. J Nutr Health Aging 2009;13:350–2.

Galasko D, Bennet D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. Alzheimer Dis Assoc Disord 1997;11 Suppl 2:S33–9.

Gauthier S, Reisberg B, Zaudig M, et al., on behalf of the participants of the International Psychogeriatric Association Expert Conference on mild cognitive impairment. Mild cognitive impairment. Lancet 2006;367:1262–70.

Goveas JS, Xie C, Ward BD, et al. Recovery of hippocampal recovery connectivity correlates with cognitive improvement in mild Alzheimer's disease patients treated with donepezil assessed by resting-state fMRI. J Magn Reson Imaging 2011;34:764–73.

Grecius B, Srivastava AL, Reiss V, et al. Default-mode network activity distinguishes Alzheimer's disease from healthy aging. Proc Natl Acad Sci U.S.A. 2004;101:4637–42.

Hang Y, Chiao P, Sevigny J, et al. Pharmacokinetic and pharmacodynamic (PK-PD) assessment and covariate analysis of aducanumab (BIIB037) in a randomized, double-blind, placebo-controlled, Phase 1b study (PRIME) in subjects with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Poster presentation. March 2015. Nice, France.

Hardy J, Selkoe DJ. The amyloid hypothesis of Alzheimer's disease: progress and problems on the road to therapeutics. Science 2002;297:353–6.

Hsiung GYR, Feldman HH. Pharmacological treatment in moderate-to-severe Alzheimer's disease. Expert Opin Pharmacother 2008;9:2575–82.

Jack CR Jr, Knopman DS, Jagust WJ, et al. Hypothetical model of dynamic biomarkers of the Alzheimer's pathological cascade. Lancet Neurol 2010;9:119–28.

Kiresuk TJ, Smith A, Cardillo JE. Goal Attainment Scaling: applications, theory, and measurement. Hillsdale (NJ): Lawrence Erlbaum Associates 1994.

Kobak KA. Inaccuracy in clinical trials: effects and methods to control inaccuracy. Curr Alzheimer Res 2010;7:637–41.

Kress BT, Iliff JJ, Xia M, et al. Impairment of Paravascular Clearance Pathways in the Aging Brain. An Neurol 2014;76:845–61.

Kurz A, Perneczky P. Amyloid clearance as a treatment target against Alzheimer's disease. J Alzheimers Dis 2011;24 Suppl 2:61–73.

Li T-Q, Wahlund L-O. The search for neuroimaging biomarkers of Alzheimer's disease with advanced MRI techniques. Acta Radiol 2011;52:211–22.

Logsdon RG, Gibbons, LE, McCurry SM, et al. Quality of life in Alzheimer's disease: patient and caregiver reports. J Mental Health Aging 1999;5:21–32.

Lopresti BJ, Klunk WE, Mathis CA, et al. Simplified quantification of Pittsburgh Compound B amyloid imaging PET studies: a comparative analysis. J Nucl Med 2005;46:1959–72.

Logsdon RG, Gibbons LE, McCurry SM, et al. Assessing quality of life in older adults with cognitive impairment. Psychosomatic Med 2002;64:510–9.

Lorenzi M, Beltramello A, Mercuri NB, et al. Effect of memantine on resting state default mode network activity in Alzheimer's disease. Drugs Aging 2011;28:205–17.

McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

Mesterton J, Wimo A, By A, et al. Cross sectional observational study on the societal costs of Alzheimer's disease. Cur Alzheimer Res 2010;7:358–67.

Mohs RC, Doody RS, Morris JC, et al. A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481–8.

Mungas D, Reed BR, Tomaszewski-Farias S, et al. Criterion-referenced validity of a neuropsychological test battery: equivalent performance in elderly Hispanics and non-Hispanic Whites. J Intl Neuropsychol Soc 2005;11:620–30.

Neugroschl J, Sano M. Current treatment and recent clinical research in Alzheimer's disease. Mt Sinai J Med 2010;77:3–16.

O'Bryant SE, Lacritz LH, Hall J, et al. Validation of new interpretive guidelines for the Clinical Dementia Rating Scale Sum of Box Score in the National Alzheimer's Coordinating Center Database. Arch Neurol 2010:67;746–9.

Ostrowitzki S, Deptula D, Thurfjell L, et al. Mechanism of amyloid removal in patients with Alzheimer's disease treated with gantenerumab. Arch Neurol 2012;69: 198–207.

Prince M, Bryce R, Albanese E, et al. The global prevalence of dementia: a systematic review and meta-analysis. Alzheimers Dement 2013:9;63–75.

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–64.

Salloway S, Sperling R, Gilman S, et al., on behalf of the bapineuzumab 201 Clinical Trial Investigators. A phase 2 multiple ascending dose trial of bapineuzumab in mild to moderate Alzheimer's disease. Neurology 2009:73:2061–70.

Salloway S, Sperling R, Fox N, et al., Two Phase 3 Trials of Bapineuzumab in Mild-to-Moderate Alzheimer's Disease. N Engl J Med 2014;370:322–33.

Schneider LS, Dagerman KS, Higgins JP, et al. Lack of evidence for the efficacy of memantine in mild Alzheimer's disease. Arch Neurol 2011;68:991–8.

Selkoe DJ. Alzheimer's disease in the beginning. Nature 1991;354:432–3.

Selkoe DJ, Mandelkow E, Holtzman D. Deciphering Alzheimer disease. Cold Spring Harb Perspect Med 2012;2:a011460.

Serrano-Pozo A, William CM, Ferrer I, et al. Beneficial effect of human anti-amyloid-β active immunization on neurite morphology and tau pathology. Brain 2010;133 (Pt 5):1312–27.

Sevigny JJ, Peng Y, Liu L. Item analysis of ADAS-Cog: effect of baseline cognitive impairment in a clinical AD trial. Am J Alzheimer's Disease Other Dement 2010:25:119–24.

Sevigny J, Chiao P, Williams L, et al. Randomized, double-blind, Phase 1b study of BIIB037 in patients with prodromal or mild Alzheimer's disease. 12th International Congress on Alzheimer's and Parkinson's Disease. Symposium 26. March 2015. Nice, France.

Shaw LM, Vanderstichele H, Knapik-Czajka M, et al. Cerebrospinal fluid biomarker signature in Alzheimer's Disease Neuroimaging Initiative subjects. Ann Neurol 2009;65:403–13.

Sheline YI, Raichle ME. Resting state functional connectivity in preclinical Alzheimer's disease. Biol Psychiatry 2013;74:340–7.

Sheline YI, Raichle ME, Synder AZ, et al. Amyloid plaques disrupt resting state default mode network connectivity in cognitively normal elderly. Biol Psychiatry 2010;67:584–7.

Siderowf A, Joshi A, Lu M, et al. Lack of substantial progression of cognitive deficits in patients with negative amyloid imaging: implications for clinical trials [abstract]. Neurology 2013;80:Abstract P01.016.

Spackman DE, Kadiyala S, Neumann PJ, et al. The validity of dependence as a health outcome measure in Alzheimer's disease. Am J Alzheimers Dis Other Dement 2013;28:245–52.

Sperling R, Salloway S, Raskind M, et al. A randomized, double-blind, placebo-controlled clinical trial of intravenous bapineuzumab in patients with mild to moderate Alzheimer's disease who are apolipoprotein ε4 carriers (presented at the 16th Congress of the European Federation of Neurological Societies, Stockholm, Sweden, 11 September 2012). Eur J Neurol 2012a:19 (Suppl 1):70.

Sperling R, Salloway S, Brooks DJ, et al. Amyloid-related imaging abnormalities in patients with Alzheimer's disease treated with bapineuzumab: a retrospective analysis. Lancet Neurol 2012b;11:241–9.

Sperling RA, Karlawish J, Johnson KA. Preclinical Alzheimer disease — the challenges ahead. Nat Rev Neurol 2013;9:54–8.

Solé-Padullés C, Bartrés-Faz D, Lladó A, et al. Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memory encoding in Alzheimer's disease. J Clin Psychopharmacol 2013;33:199–205.

Stern Y, Albert SM, Sano M, et al. Assessing patient dependence in Alzheimer's disease. J Gerontol 1994;49:M216–22.

U.S. Veterans Health Administration (AVH), Pharmacy Benefits. Estimated cases of dementia in VA patient population. All levels of severity. Available at U.S. Department of Veterans Affairs Web site http://www.4.va.gov/HEALTHPOLICYPLANNING/dementia/patient.pdf. Accessed on 13 August 2013.

Vellas B, Coley N, Andrieu S. Disease modifying trials in Alzheimer's disease: perspectives for the future. J Alzheimers Dis 2008;15:289–301.

Weller RO, Boche D, Nicoll JAR. Microvasculature changes and cerebral amyloid angiopathy in Alzheimer's disease and their potential impact on therapy. Acta Neuropathol 2009;118:87–102.

Wild D, Grove A, Martin M, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value in Health 2005;8:94–104.

Wimo A, Winblad B, Stöffler A, et al. Resource utilization and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003;21:327–40.

World Health Organization (WHO). The global burden of disease: 2004 update. Geneva, Switzerland: World Health Organization, 2008. Available at: http://www.who.int/healthinfo/global_burden_disease/GBD_report_2004update_full.pdf. Accessed 25 July 2013.

World Health Organization (WHO), Alzheimer's Disease International Association. Dementia: a public health priority. WHO report 2012. Geneva, Switzerland: World Health Organization, 2012. Available at: http://www.who.int/about/licensing/copyright_form/e/index.html. Accessed 20 August 2013.

Zarit SH, Zarit JM. The memory and behavior problems checklist and the burden interview. Gerontology Center, Penn State University, 1990.

Zhang RY, Leon AC, Chuang-Stein C, et al. A new proposal for randomized start design to investigate disease-modifying therapies for Alzheimer's disease. Clin Trials 2011;8:5–14.

Appendix 1
Schedule of Assessments Part 1

Table 1: Year 1 Assessments

Assessment/ Procedure	Screening	BL		Treatment Period													Unsch [a]
	Wk –1 to Wk –8	Day 1	Day 4 (± 2 days)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	
Dose number		1		2	3	4	5	6	7	8	9	10	11	12	13	14	
Informed consent(s) [b]	x																
Review of inclusion and exclusion criteria	x																
Medical history, personal status, and demographics [c]	x																
Physical exam	x														x		x
Neurologic exam	x														x		x
Clinical genotyping sample	x [d]																
RCR DNA sample [e]		x															
RCR RNA sample [e]		x															
RCR plasma sample [e]		x															
Vital signs [f]	x [f]	x [f]		x	x	x	x	x	x	x	x	x	x	x	x	x	x [f]
12-Lead electrocardiogram [g]	x	x													x		x
Serum chemistry [h] and hematology [i]	x [h]	x							x						x [h]		x
PK plasma sample [j]		x	x	x	x	x			x						x		x
Anti-drug antibody sample		x [j]		x	x	x			x						x		x
Coagulation (prothrombin time)	x																x
Urine sample for drugs of abuse	x																x
Urinalysis [k]	x																x

Appendix 1
Schedule of Assessments Part 1 (cont.)

Table 1: Year 1 Assessments (cont.)

Assessment/ Procedure	Screening	BL		Treatment Period													Unsch [a]
	Wk–1 to Wk–8	Day 1	Day 4 (±2 days)	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	Wk 36	Wk 40	Wk 44	Wk 48	Wk 52	
Dose Number		1		2	3	4	5	6	7	8	9	10	11	12	13	14	
Urine pregnancy test [l]	x	x [l]		x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x [l]	x
Lumbar puncture [m, n] and CSF sampling [n, o]	x [n, o]															x [o]	x
MRI scan [p]	x [n, q, r]								x [q, r]			x			x [q, r]		x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant meds	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ADAS-Cog13	x	x							x						x		x
CDR [u]	x	x							x						x		x
ADCS-ADL [u]	x	x							x			x			x		x
MMSE	x	x							x			x			x		x
NPI [u]		x							x						x		x
GDS	x																x
QoL-AD		x							x						x		x
ZCI-AD [u]		x													x		x
Dependence Scale [u]		x													x		x
SymptomGuide™ Facilitated GAS (if applicable) [s, u]		x			x				x						x		x
C-SSRS		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x
RUD-Lite [u]		x													x		x
Study drug administration [t]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1
Schedule of Assessments Part 1 (cont.)

Table 1: Year 1 Assessments (cont.)

AD = Alzheimer's Disease; ADAS-Cog = Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; BL = Baseline; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale ; GAS = Goal Attainment Scaling; GDS = Geriatric Deterioration Scale; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; NPI = Neuropsychiatric Inventory; PK = pharmacokinetic; QoL = quality of life; RCR = Roche Clinical Repository; RUD = Resource Utilization Dementia; Wk = Week; Unsch = Unscheduled; ZCI = Zarit Caregiver Interview.

Note: On the baseline visit, all safety assessments must be conducted on the day of dosing and all other assessments may be conducted up to 7 days earlier. On day 4, the visit window is ± 1 day. The visit window is ± 7 days for all other visits.

[a] For patients who terminate early, the assessments from Week 104 should be used.

[b] The WN28745-PET substudy & WN28745-Cardiac PET substudy are optional, and patients who elect to participate must sign a separate informed consent.

[c] Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol and drugs of abuse; and all medications (e.g., prescription drugs, over-the-counter drugs, herbal/homeopathic remedies, nutritional supplements) used by the patient within 6 months prior to the screening visit. Demographics include age, sex, and self-reported race/ethnicity.

[d] At screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction for analysis of APOE ε4 status and Fcγ receptor genotype.

[e] Optional RCR samples for exploratory analysis from consenting patients should be obtained at the same time that the blood samples are obtained.

[f] Vital signs include heart rate (HR) and blood pressure (BP) and at screening, Day 1, and unscheduled visits also include body temperature. The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected at screening and week 104 visits.

[g] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[h] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). During the screening period (Week – 1 to Week – 8), and at Weeks 48 and 104, hemoglobin A_{1C}, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

[i] Hematology includes hemoglobin, hematocrit, red blood cell (with morphology), WBCs, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[j] The baseline sample will be obtained prior to first dose. All pharmacokinetic (PK) samples except the Day 4 sample should be obtained just before administration of study drug (gantenerumab or placebo) or during the specified visits, if possible. Accurate recording of the time of study drug administration and PK sampling is critical.

[k] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive.

Appendix 1
Schedule of Assessments Part 1 (cont.)

Table 1: Year 1 Assessments (cont.)

[l] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[m] Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.

[n] CSF sampling and MRI (and PET scan if the patient is enrolled in any of the PET substudies) at screening should be performed once all other screening results are available and none exclude the patient from the trial. For patients enrolled in any of the PET substudies, PET may be performed after the lumbar puncture and prior to when CSF results are received; there is no requirement for CSF results to be available before the PET. After aliquoting the required samples, any remaining CSF fluid from consenting patients will be kept for future RCR biomarker research.

[o] CSF samples are mandatory at screening; collection at Week 52 is optional.

[p] MRI should not be performed for 3 days following a lumbar puncture. MRI scans must be performed within a maximum of 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[q] Includes volumetric MRI outcome measures.

[r] Includes functional MRI outcome measures.

[s] The SymptomGuide™ Facilitated GAS will be conducted at investigational sites in French and English speaking countries.

[t] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients as SC injection to the abdomen. Study personnel administering study drug must not be involved with any efficacy assessments or safety evaluations. Following the first four doses, patients should be observed for a minimum of 2 hours after dosing; for the remaining doses, patients should be observed for a minimum of 1 hour. On days when only safety is being assessed, patients may have the option to have study drug administered and applicable safety assessments conducted at a prearranged location away from the site by a trained health care professional if consent is obtained.

[u] Scale requires caregiver input or support.

Appendix 1
Schedule of Assessments Part 1 (cont.)

Table 2: Year 2 Assessments

Assessment/ Procedure	Treatment Period												Follow-Up		Additional Follow-Up	Unsch [a]
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104 or Early Term [a]	Wk 116	Wk 152	
Dose Number	15	16	17	18	19	20	21	22	23	24	25	26				
Physical examination													x	x	x	x
Neurologic examination													x	x	x	x
Vital signs [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [b]
12-Lead ECG [c]													x		x	x
Serum chemistry [d] and hematology [e, f]					x								x [d]		x	x
PK plasma sample					x								x	x		x
Anti-drug antibody sample					x								x	x		x
Urinalysis [g]																x
Urine pregnancy test [h]	x	x	x	x	x	x	x	x	x	x	x	x				x
Lumbar puncture [i, j] and CSF sampling [j, k]													x [k]		x [k]	x
MRI scan [l]													x [m, n]		x [m]	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Concomitant meds	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
CDR [o]					x								x		x	x
ADAS-Cog13					x								x	x	x	x
ADCS-ADL [o]		x			x			x			x		x	x	x	x
NPI [o]					x								x		x	x
MMSE		x			x			x			x		x	x	x	x

Appendix 1
Schedule of Assessments Part 1 (cont.)

Table 2: Year 2 Assessments (cont.)

Assessment/ Procedure	Treatment Period												Follow-Up		Additional Follow-Up	Unsch [a]
	Wk 56	Wk 60	Wk 64	Wk 68	Wk 72	Wk 76	Wk 80	Wk 84	Wk 88	Wk 92	Wk 96	Wk 100	Wk 104 or Early Term [a]	Wk 116	Wk 152	
Dose number	15	16	17	18	19	20	21	22	23	24	25	26				
C-SSRS	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Dependence Scale [o]													x		x	x
RUD-Lite [o]													x		x	x
ZCI-AD [o]													x		x	x
QoL-AD					x						x		x		x	x
SymptomGuide™ Facilitated GAS (if applicable) [o, p]					x								x		x	x
Study drug administration [q]	x	x	x	x	x	x	x	x	x	x	x	x				

AD=Alzheimer's Disease; ADAS-Cog=Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR=Clinical Dementia Rating; C-SSRS= Columbia-Suicide Severity Rating Scale; ECG=electrocardiogram; MMSE=Mini Mental State Examination; MRI=magnetic resonance imaging; NPI=Neuropsychiatric Inventory; PK=pharmacokinetic; QoL=quality of life; RUD=Resource Utilization Dementia; Wk=Week; Unsch=Unscheduled; ZCI=Zarit Caregiver Interview.

Note: The visit window is ± 7 days for all visits.

[a] For patients who terminate early, the unscheduled visit assessments should be used.

[b] Vital signs include heart rate (HR) and blood pressure (BP) and at unscheduled visits also include body temperature. The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected at screening and week 104 visits.

[c] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[d] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Week 104, hemoglobin A_{1C}, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

Table 2: Year 2 Assessments (cont.)

[e] Hematology includes hemoglobin, hematocrit, red blood cell (with morphology), WBCs, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A pharmacokinetic (PK) sample will be obtained at unscheduled visits.

[g] Urinalysis will be performed at the site by dipstick for blood, protein, glucose, and pH. Microscopic examination performed at the central laboratory if blood and/or protein results are positive or strongly positive.

[h] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[i] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon [12:00 p.m.]) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.

[j] For patients enrolled in any of the PET substudies, PET may be performed after the lumbar puncture and prior to CSF results are received; there is no requirement for CSF results to be available before the PET. After aliquoting the required samples, any remaining CSF fluid from consenting patients will be kept for future RCR biomarker research.

[k] CSF samples are mandatory at Week 104; collection at Week 152 is optional.

[l] MRI should not be performed for 3 days following a lumbar puncture. MRI scans must be performed 20 days after dose administration and results available and reviewed before the next scheduled dose. The final MRI should be performed ~4 weeks before the final follow-up visit to allow for review before the final visit.

[m] Includes volumetric MRI outcome measures.

[n] Includes functional MRI outcome measures.

[o] Scale requires caregiver input or support.

[p] The SymptomGuide™ Facilitated GAS will be conducted at investigational sites in French- and English-speaking countries.

[q] Study drug administration should be performed only after all assessments/rating scales for the patient are completed (unless indicated otherwise). Study drug will be administered to patients as SC injection to the abdomen. Study personnel administering study drug must not be involved with any efficacy assessments or safety evaluations. Following the first four doses, patients should be observed for a minimum of 2 hours after dosing; for the remaining doses, patients should be observed for a minimum of 1 hour. On days when only safety is being assessed, patients may have the option to have study drug administered and applicable safety assessments conducted at a prearranged location away from the site by a trained health care professional if consent is obtained.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2

Table 1: Patients Previously on 225 mg Gantenerumab: Carriers

Assessment/ Procedure	Pre-OLE	Treatment Period																Follow-Up		
		OLD 1[a]	OLW 4	OLW 8	OLW 12	OLW 16	OLW 20	OLW 24	OLW 28	OLW 32	OLW 36	OLW 40	OLW 44	OLW 48	OLW 52	OLW 53	OLW 56–100	OLW 101	OLW 104[b]	OLW 116	UV
Dose number		1	2	3	4	5	6	7	8	9	10	11	12	13	14		15–26				
Dose level (mg)		450	450	900	900	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200		1200				
Informed consent(s)[c]	x																				
MRI[d]			x		x			x				x			x[e]		x[f]		x[e]		x
APOE results[g]	x																				
Vital signs[h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ECG[i]		x												x					x		x
Serum chemistry and hematology[j]		x[k]						x						x					x		x
PK plasma sample[l]			x		x		x									x		x	x	x	x
ADA sample[l]			x																x	x	x
Urine pregnancy test[m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Lumbar puncture[n]															x				x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ADAS-Cog13		x[k]													x				x		x
CDR		x[k]													x				x		x
ADCS-ADL		x[k]													x				x		x
MMSE		x[k]													x				x		x
C-SSRS[o]		x						x						x			x[o]		x		x
PET Scans[c]	x[p]														x				x		x
Physical Exam	x[q]																		x		x

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 1: Patients Previously on 225 mg Gantenerumab: Carriers (cont.)

ADA = anti-drug antibody; ADAS-Cog = Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; ICF = Informed Consent Form; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLD 1 = Open Label Day 1; OLE = open-label extension; OLW = Open Label Week; PET = positron emission tomography; PK = pharmacokinetic; UV = Unscheduled Visit.

Note: The visit window is ± 7 days for all visits.

[a] First open-label gantenerumab dose administered following signature of Part 2 ICF.

[b] Patients who continue OLE beyond the initial 2 years will need to complete OLE Week 104 assessments as per Table 5.

[c] Informed consents have to be signed prior to patients starting open label including an ICF to the PET substudy for those patients participating in the PET substudies. Patients who complete the initial 2 years of OLE and who will not be continuing treatment extension will have their last PET scan 1 year after their last dose.

[d] MRI scans during up-titration (including the MRI scan 3 months post 1200 mg) or following re-dosing after ARIA findings have resolved, must be performed 10–20 days after dose administration. Other scheduled MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[e] Includes volumetric and functional MRI outcome measures.

[f] A safety MRI should be collected at Week 76.

[g] APOE results (carrier vs. non-carriers) should be revealed and appropriate counseling offered to the patient.

[h] Vital signs include heart rate (HR) and blood pressure (BP). The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected at OLE Week 104 visit.

[i] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[j] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At OLE Weeks 48 and 104, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

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

[k] Serum chemistry and hematology and listed efficacy scales should be obtained prior to first dose open label if these assessments were obtained more than 6 months ago.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 1: Patients Previously on 225 mg Gantenerumab: Carriers (cont.)

[l] At all visits when a PK and ADA samples (including PK obtained for ARIA findings) are needed, the samples should be obtained just before administration of gantenerumab, unless at weeks 53 and 101. Accurate recording of the time of study drug administration and PK sampling is critical.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[n] Lumbar puncture at Weeks 52 and 104 are optional. Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.

[o] From Weeks 56–100, C-SSRS should only be obtained at week 72. C-SSRS may be obtained at any time deemed necessary by the investigator.

[p] Patients participating in the PET substudies and whose last PET was more than 9 months ago will need a pre-OLE PET scan prior to starting the OLE.

[q] Physical and Neurologic Exam prior to OLE is optional.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 2: Patients Previously on 225 mg Gantenerumab: Non-Carriers

Assessment/ Procedure	Pre-OLE	Treatment Period																Follow-Up		
		OLD 1[a]	OLW 4	OLW 8	OLW 12	OLW 16	OLW 20	OLW 24	OLW 28	OLW 32	OLW 36	OLW 40	OLW 44	OLW 48	OLW 52	OLW 53	OLW 56–100	OLW 101	OLW 104[b]	OLW 116	UV
Dose number		1	2	3	4	5	6	7	8	9	10	11	12	13	14		15–26				
Dose level (mg)		600	600	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200		1200				
Informed consent(s)[c]	x																				
MRI[d]			x			x						x			x[e]		x[f]		x[e]		x
APOE results[g]	x																				
Vital signs[h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ECG[i]		x												x					x		x
Serum chemistry and hematology[j]		x[k]						x						x					x		x
PK plasma sample[l]			x		x											x		x	x	x	x
ADA sample[l]			x																x	x	x
Urine pregnancy test[m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Lumbar puncture[n]															x				x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ADAS-Cog13		x[k]													x				x		x
CDR		x[k]													x				x		x
ADCS-ADL		x[k]													x				x		x
MMSE		x[k]													x				x		x
C-SSRS[o]		x						x						x			x[o]		x		x
PET Scans[c]	x[p]														x				x		x
Physical Exam	x[q]																		x		x

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 2: Patients Previously on 225 mg Gantenerumab: Non-Carriers (cont.)

ADA = anti-drug antibody; ADAS-Cog = Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; ICF = Informed Consent Form; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLD 1 = Open Label Day 1; OLW = Open Label Week; OLE = open-label extension; PET = positron emission tomography; PK = pharmacokinetic; UV = Unscheduled Visit.

Note: The visit window is ± 7 days for all visits.

[a] First open-label gantenerumab dose administered following signature of Part 2 ICF.

[b] Patients who continue OLE beyond the initial 2 years will need to complete OLE Week 104 assessments as per Table 5.

[c] Informed consents have to be signed prior to patients starting open label including an ICF to the PET substudy for those patients participating in the PET substudies. Patients who complete the initial 2 years of OLE and who will not be continuing treatment extension will have their last PET scan 1 year after their last dose.

[d] MRI scans during up-titration (including the MRI scan 3 months post 1200 mg) or following re-dosing after ARIA findings have resolved, must be performed 10–20 days after dose administration. Other scheduled MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[e] Includes volumetric and functional MRI outcome measures.

[f] A safety MRI should be collected at Week 76.

[g] APOE results (carrier vs. non-carriers) should be revealed and appropriate counseling offered to the patient.

[h] Vital signs include heart rate (HR) and blood pressure (BP). The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected pre OLE and Week 104 visits.

[i] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[j] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Weeks 48 and 104, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

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

[k] Serum chemistry and hematology and listed efficacy scales should be obtained prior to first dose open label if these assessments were obtained more than 6 months ago.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 2: Patients Previously on 225 mg Gantenerumab: Non-Carriers (cont.)

[l] At all visits when a PK and ADA samples (including PK obtained for ARIA findings) are needed, the samples should be obtained just before administration of gantenerumab, unless at weeks 53 and 101. Accurate recording of the time of study drug administration and PK sampling is critical.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[n] Lumbar puncture at Weeks 52 and 104 are optional. Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.

[o] From Weeks 56–100, C-SSRS should only be obtained at week 72. C-SSRS may be obtained at any time deemed necessary by the investigator.

[p] Patients participating in the PET substudies and whose last PET was more than 9 months ago will need a pre-OLE PET scan prior to starting the OLE.

[q] Physical and Neurologic Exam prior to OLE is optional.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 3: Patients Previously on 105 mg Gantenerumab or Placebo: Carriers

Assessment/ Procedure	Pre-OLE	Treatment Period																Follow-Up		
		OLD 1[a]	OLW 4	OLW 8	OLW 12	OLW 16	OLW 20	OLW 24	OLW 28	OLW 32	OLW 36	OLW 40	OLW 44	OLW 48	OLW 52	OLW 53	OLW 56–100	OLW 101	OLW 104[b]	OLW 116	UV
Dose number		1	2	3	4	5	6	7	8	9	10	11	12	13	14		15–26				
Dose level (mg)		225	225	450	450	900	900	1200	1200	1200	1200	1200	1200	1200	1200		1200				
Informed consent(s)[c]	x																				
MRI[d]			x		x		x			x		x[e]			x[f]		x[g]		x[f]		x
APOE results[h]	x																				
Vital signs[i]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ECG[j]		x												x					x		x
Serum chemistry and hematology[k]								x						x					x		x
PK plasma sample[l]			x		x		x		x							x		x	x	x	x
ADA sample[l]			x																x	x	x
Urine pregnancy test[m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Lumbar puncture[n]															x				x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ADAS-Cog13		x[o]													x				x		x
CDR		x[o]													x				x		x
ADCS-ADL		x[o]													x				x		x
MMSE		x[o]													x				x		x
C-SSRS[p]		x						x						x			x[p]		x		x
PET Scans[c]	x[q]														x				x		x
Physical Exam[r]	x[r]																		x		x

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 3: Patients Previously on 105 mg Gantenerumab or Placebo: Carriers (cont.)

ADA = anti-drug antibody; ADAS-Cog = Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; ICF = Informed Consent Form; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLD 1 = Open Label Day 1; OLW = Open Label Week; OLE = open-label extension; PET = positron emission tomography; PK = pharmacokinetic; UV = Unscheduled Visit.

Note: The visit window is ± 7 days for all visits.

[a] First open-label gantenerumab dose administered following signature of Part 2 ICF.

[b] Patients who continue OLE beyond the initial 2 years will need to complete OLE Week 104 assessments as per Table 5.

[c] Informed consents have to be signed prior to patients starting open label including an ICF to the PET substudy for those patients participating in the PET substudies. Patients who complete the initial 2 years of OLE and who will not be continuing treatment extension will have their last PET scan 1 year after their last dose.

[d] MRI scans during up-titration (including the MRI scan 3 months post 1200 mg) or following re-dosing after ARIA findings have resolved, must be performed 10–20 days after dose administration. Other scheduled MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[e] Optional MRI.

[f] Includes volumetric and functional MRI outcome measures.

[g] A safety MRI should be collected at Week 76.

[h] APOE results (carrier vs. non-carriers) should be revealed and appropriate counseling offered to the patient.

[i] Vital signs include heart rate (HR) and blood pressure (BP). The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected pre OLE and Week 104 visits.

[j] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[k] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Weeks 48 and 104, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

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

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 3: Patients Previously on 105 mg Gantenerumab or Placebo: Carriers (cont.)

[l] At all visits when a PK and ADA samples (including PK obtained for ARIA findings) are needed, the samples should be obtained just before administration of gantenerumab, unless at weeks 53 and 101. Accurate recording of the time of study drug administration and PK sampling is critical.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[n] Lumbar puncture at Weeks 52 and 104 are optional. Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.

[o] Serum chemistry and hematology and listed efficacy scales should be obtained prior to first dose open label if these assessments were obtained more than 6 months ago.

[p] From Weeks 56–100, C-SSRS should only be obtained at week 72. C-SSRS may be obtained at any time deemed necessary by the investigator.

[q] Patients participating in the PET substudies and whose last PET was more than 9 months ago will need a pre-OLE PET scan prior to starting the OLE.

[r] Physical and Neurologic Exam prior to OLE is optional.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 4: Patients Previously on 105 mg Gantenerumab or Placebo: Non-Carriers

Assessment/ Procedure	Pre-OLE	Treatment Period																Follow-Up		
		OLD 1[a]	OLW 4	OLW 8	OLW 12	OLW 16	OLW 20	OLW 24	OLW 28	OLW 32	OLW 36	OLW 40	OLW 44	OLW 48	OLW 52	OLW 53	OLW 56–100	OLW 101	OLW 104[b]	OLW 116	UV
Dose number		1	2	3	4	5	6	7	8	9	10	11	12	13	14		15–26				
Dose level (mg)		300	300	600	600	1200	1200	1200	1200	1200	1200	1200	1200	1200	1200		1200				
Informed consent(s)[c]	x																				
MRI[d]			x		x			x				x			x[e]		x[f]		x[e]		x
APOE results[g]	x																				x
Vital signs[h]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ECG[i]		x												x					x		x
Serum chemistry and hematology[j]		x[k]						x						x					x		x
PK plasma sample[l]			x		x		x									x		x	x	x	x
ADA sample[l]			x																x	x	x
Urine pregnancy test[m]		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Lumbar puncture[n]															x				x		x
Adverse events		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
Concomitant meds		x	x	x	x	x	x	x	x	x	x	x	x	x	x		x		x	x	x
ADAS-Cog13		x[k]													x				x		x
CDR		x[k]													x				x		x
ADCS-ADL		x[k]													x				x		x
MMSE		x[k]													x				x		x
C-SSRS[o]		x						x						x			x[o]		x		x
PET Scans[c]	x[p]														x				x		x
Physical Exam[q]	x[q]																		x		x

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 4: Patients Previously on 105 mg Gantenerumab or Placebo: Non-Carriers (cont.)

ADA = anti-drug antibody; ADAS-Cog = Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; APOE = apolipoprotein E; CDR = Clinical Dementia Rating; C-SSRS = Columbia-Suicide Severity Rating Scale; ICF = Informed Consent Form; MMSE = Mini Mental State Examination; MRI = magnetic resonance imaging; OLD 1 = Open Label Day 1; OLW = Open Label Week; OLE = open-label extension; PET = positron emission tomography; PK = pharmacokinetic; UV = Unscheduled Visit.

Note: The visit window is ± 7 days for all visits.

[a] First open-label gantenerumab dose administered following signature of Part 2 ICF.

[b] Patients who continue OLE beyond the initial 2 years will need to complete OLE Week 104 assessments as per Table 5.

[c] Informed consents have to be signed prior to patients starting open label including an ICF to the PET substudy for those patients participating in the PET substudies. Patients who complete the initial 2 years of OLE and who will not be continuing treatment extension will have their last PET scan 1 year after their last dose.

[d] MRI scans during up-titration (including the MRI scan 3 months post 1200 mg) or following re-dosing after ARIA findings have resolved, must be performed 10–20 days after dose administration. Other scheduled MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[e] Includes volumetric and functional MRI outcome measures.

[f] A safety MRI should be collected at Week 76.

[g] APOE results (carrier vs. non-carriers) should be revealed and appropriate counseling offered to the patient.

[h] Vital signs include heart rate (HR) and blood pressure (BP). The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will only be collected pre OLE and Week 104 visits.

[i] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[j] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At Weeks 48 and 104, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

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

[k] Serum chemistry and hematology and listed efficacy scales should be obtained prior to first dose open label if these assessments were obtained more than 6 months ago.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 4: Patients Previously on 105 mg Gantenerumab or Placebo: Non-Carriers (cont.)

[l] At all visits when a PK and ADA samples (including PK obtained for ARIA findings) are needed, the samples should be obtained just before administration of gantenerumab, unless at Weeks 53 and 101. Accurate recording of the time of study drug administration and PK sampling is critical.

[m] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

[n] Lumbar puncture at Weeks 52 and 104 are optional. Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10-20 days after dosing.

[o] From Weeks 56–100, C-SSRS should only be obtained at week 72. C-SSRS may be obtained at any time deemed necessary by the investigator.

[p] Patients participating in the PET substudies and whose last PET was more than 9 months ago will need a pre-OLE PET scan prior to starting the OLE.

[q] Physical and Neurologic Exam prior to OLE is optional.

Appendix 2
OLE Schedule of Assessments Part 2: Years 1 and 2 (cont.)

Table 5: For All Patients

			Additional Years				Follow-Up		
Weeks (± 7 days)		104	+4–20	+24	+28–48	+52	F1 [a]	F2 [a] *(Patients not enrolling in Study WN41874.)*	UV
Informed consent(s) [b]	x								
Dose every 4 weeks		x	x	x	x	x			
MRI [c]		x[d]		x		x	x		x
Vital signs [e]		x	x	x	x	x	x	x	x
ECG [f]		x				x	x		x
Serum chemistry and hematology [g]		x				x	x		x
PK plasma sample [h]		x				x	x	x	x
ADA sample [h]		x				x	x	x	x
Urine pregnancy test [i]		x	x	x	x	x	x	x	x
Adverse events		x	x	x	x	x	x	x	x
Concomitant meds		x	x	x	x	x	x	x	x
ADAS-Cog13		x							
CDR		x							
ADCS-ADL		x							
MMSE		x		x		x	x		x
C-SSRS [j]		x		x		x	x		x
PET Scans		x				x[k]			
Physical Examination		x				x	x		x
Lumbar puncture		*x* [l]							

Appendix 2
OLE Schedule of Assessments: Part 2: Years 1 and 2 (cont.)

Table 5: For All Patients (cont.)

ADA=anti-drug antibody; ADAS-Cog=Alzheimer's Disease Activity Scale-Cognitive; ADCS-ADL=Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR=Clinical Dementia Rating; *CSF=cerebrospinal fluid;* C-SSRS=Columbia-Suicide Severity Rating Scale; ICF=Informed Consent Form; MMSE=Mini Mental State Examination; MRI=magnetic resonance imaging; PET=positron emission tomography; PK=pharmacokinetic; F1=Follow-Up 1; F2=Follow-Up 2 (+16 weeks after last dose); UV=Unscheduled Visit.

Note: The visit window is ± 7 days for all visits. *However, the minimum time between doses is 21 days, and the target day for each visit is timed with respect to baseline, not the prior visit.*

[a] Follow-up visits should be obtained 4 and 16 weeks after last dose. *The follow-up visit at 16 weeks is not required for patients who enroll in Study WN41874 (open-label rollover study).*

[b] Patients who continue OLE beyond the initial 2 years to the treatment extension should sign ICF prior to Week 104.

[c] MRI scans during up-titration (including the MRI scan 3 months post 1200 mg) or following re-dosing after ARIA findings have resolved, must be performed 10–20 days after dose administration. Other scheduled MRI scans must be performed within 20 days after dose administration and results made available and reviewed before the next scheduled dose. The final MRI should be performed approximately 4 weeks before the final follow-up visit to allow for review before the final visit.

[d] Includes volumetric and functional MRI outcome measures.

[e] Vital signs include heart rate (HR) and blood pressure (BP). The same arm should be used for all blood pressure measurements. HR and BP should not be measured unless 15 minutes have passed since the last blood draw. Weight will be collected yearly at the time of physical exam.

[f] Perform after the patient has been in a supine position for 5 minutes. ECGs for each patient should be obtained from the same machine whenever possible and performed prior to any blood draws, brain MRI scans, and lumbar puncture.

[g] Serum chemistry includes AST/SGOT, ALT/SGPT, alkaline phosphatase, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). At OLE Weeks 48 and 104, hemoglobin A1C, folic acid, vitamin B12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed.

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

[h] At all visits where PK and ADA samples (including PK obtained for ARIA findings) are needed, the samples should be obtained just before administration of gantenerumab. Accurate recording of the time of study drug administration and PK sampling is critical.

[i] Females of childbearing potential (including those who have had a tubal ligation) must have a urine pregnancy test performed at the site prior to each dose administration. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

Appendix 2
OLE Schedule of Assessments: Part 2: Years 1 and 2 (cont.)

Table 5: For All Patients (cont.)

[j] C-SSRS should be obtained every 6 months or at any time deemed necessary by the investigator.

[k] Patients participating in the PET substudy will have a final PET scan at OLE Week 156.

[l] *Lumbar puncture at Week 104 is optional. Lumbar puncture must be performed in the morning (between 8:00 a.m. and 12:00 p.m.) to minimize potential diurnal variation of CSF parameters. Lumbar puncture should be performed 10–20 days after dosing.*

Appendix 3
NINCDS/ARDRA Criteria for Mild Alzheimer's Disease

I. The criteria for the clinical diagnosis of PROBABLE AD include:

Dementia established by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychologic test;
Deficits in two or more areas of cognition;
Progressive worsening of memory and other cognitive functions;
No disturbance of consciousness;
Onset between the ages 40 and 90, most often age 65; and
Absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

II. The diagnosis of PROBABLE AD is supported by:

Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia),

Impaired activities of living and altered patterns of behavior,

Family history of similar disorders, particularly if confirmed neuropathologically; and

Laboratory results of:

Normal lumbar puncture as evaluated by standard techniques,
Normal pattern or nonspecific changes in EEG, such as increased slow-wave activity, and
Evidence of cerebral atrophy on CT with progression documented by serial observation.

III. Other clinical features consistent with the diagnosis of PROBABLE AD, after exclusion of cases of dementia other than AD, include:

Plateaus in the course of progression of the illness;
Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders, and weight loss; other neurologic abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder; or
Seizures in advanced disease; and
CT normal for age

IV. Features that make the diagnosis of PROBABLE AD uncertain or unlikely include:

Sudden, apoplectic start;
Focal neurologic findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness; and
Seizures or gait disturbances at the onset or very early in the course of the illness.

V. Clinical diagnosis of PROBABLE AD:

May be made on the basis of the dementia syndrome in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and the presence of variations in the onset, in the presentation, or in the clinical course.

May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia, and

Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

Appendix 3
NINCDS/ARDRA Criteria for Mild Alzheimer's Disease (cont.)

VI.	Criteria for diagnosis of DEFINITE AD are: The clinical criteria for probable AD and Histopathologic evidence obtained from biopsy or autopsy.
VII.	Classification of AD for research purposes should specify features that may differentiate subtypes of the disorder, such as: Familial occurrence Onset before age of 65 Presence of trisomy-21 and Coexistence of other relevant conditions such as Parkinson's disease

AD = Alzheimer's disease; ARDRA = Alzheimer's Disease and Related Disorders Association; CT = computed tomography; EEG = electroencephalography; NINCDS = National Institute of Neurological and Communicative Disorders and Stroke.

Excerpted from: McKhann et al. 1984.

References

McKhann G, Drachman D, Folstein M, et al. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–44.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data

Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b StudyPET) model was built using pooled information from gantenerumab Phase 3 Study WN25203 and aducanumab Phase 1b PRIME trial. Details regarding how this population analysis was conducted and evaluated are provided in this Appendix.

2. MATERIALS AND METHODS

2.1 MODELING HYPOTHESIS

Based on the high level of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same pharmacokinetic (PK) properties in terms of disposition, metabolism, elimination, and same relationship between serum concentrations and standardized uptake value ratio (SUVr) amyloid PET reductions.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled as they were derived by using the same whole cerebellum reference region, and that the sensorimotor region used only in the composite SUVr of aducanumab was having little effect on the SUVr values.

2.2 PK-PD DATA

A PK-PD dataset for PET model building was built using information from gantenerumab trial (Study WN25203) together with information from aducanumab Phase 1b trial (Study PRIME).

2.2.1 Gantenerumab Pharmacokinetic and Positron Emission Tomography Data

2.2.1.1 Pharmacokinetic Information

Each patient taking part in Study WN25203 was sampled to measure their PK concentrations in serum at the following scheduled times: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

Those PK data from Study WN25203 were analyzed using a population PK model that was previously developed based on Phase 1 studies.

The Phase 1 PK database was composed of 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both intravenous (IV) and subcutaneous (SC) administrations, single and multiple repeated doses every 4 weeks (q4w), with a range of dose values for the repeated dose administrations from 6 to 200 mg for the IV, 105 and 225 mg for the SC, and up to 300 mg SC and 400 mg IV when administered only once. A two-compartment

model with a 0 order followed by a first-order absorption best described those Phase 1 data. Population parameter values are reported in Table A1.

Table A1. Population PK Parameters Estimated from Gantenerumab Phase 1 Data

	Mean	RSE%	BSV%	RSE%
CL (L/day)	0.336	3.20%	26.1%	6.9%
V2 (L)	3.52	5.60%	31.3%	18.5%
Q (L/day)	0.869	9.50%	55.5%	10.6%
V3 (L)	6.38	4.10%	24.9%	10%
KA (/day)	0.22	8.90%	52.2%	21.1%
D1 (/day)	0.0821	7.10%	96.6%	8.9%
F1 (-)	0.494	3.90%	42.8%	10.5%
PROP.ERR	0.196	5.40%		
ADD.ERR (µg/mL)	0.0121	21.70%		

ADD_ERR = additional error; CL = Clearance; D1 = zero order rate constant; F1 = Absolute Bioavailability; KA = Absorption rate constant; KeO = rate constant for drug transfer from serum to effect compartment; POW = power; PROP_ERR = proportional error Q = intercompartmental clearance; SLOP = Slope; V2 = Central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in NONMEM of the PK data collected from Study WN25203 and to derive for each patient the individual PK parameters, as well as an estimation of the individual average concentration over the period of observation.

2.2.1.2 Positron Emission Tomography Information

Among the 799 patients entering Study WN25203, 114 patients took part in an amyloid PET sub-study (AV-45 ligand) with scans at baseline and Weeks 20, 60, and 100. For the patients entering the second double-blind, 2-year portion of the trial (Part 2), another scan was done at Week 156.

PET data up to Week 100 (included) were considered for the PK-PD modeling investigations, and the PET database was composed of a total of 348 SUVr observations determined by using the whole cerebellum as reference region.

2.2.2 Aducanumab Pharmacokinetic and Positron Emission Tomography Pharmacodynamic Data

Aducanumab PK and PET data were extracted from a poster (n°ADPD5–2113) and from slides that were presented at the 12th International Congress on Alzheimer's Disease and Parkinson's Disease (ADPD) on March 2015 in Nice.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Those aducanumab data were collected in a randomized, double-blind, placebo-controlled Phase 1b study (PRIME) in patients with prodromal or mild Alzheimer's disease. The study design involved a parallel-group design, with a 54-week treatment period given per IV infusion q4w (14 infusions in total); four dose groups were involved on top of the placebo: 1, 3, 6, and 10 mg/kg dose group, respectively. SUVr measurements were done at baseline and Weeks 26 and 54 and were determined by using the whole cerebellum as reference region.

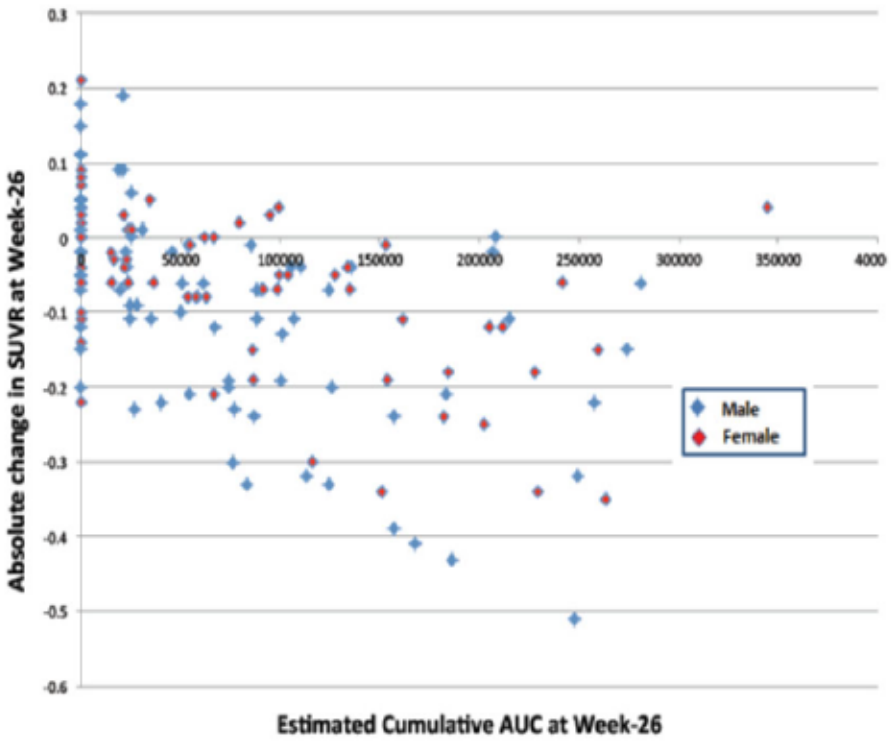
The following figures were used from the aducanumab poster and slides:

1. A figure displaying the individual absolute change in SUVr at Week 26 in function of the individual cumulative area under the concentration-time curve (AUC) at Week 2 (see Figure A1)
2. A table presenting the time course of the mean SUVr up to Week 54 by dose group (figure available upon request) (see Table A2)
3. A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure A2)

The individual data from Figure A1 were extracted and a database of 123 patients with their respective cumulative AUC at Week 26 and absolute change from baseline in SUVr. The mean data from Figure A2 were used to extrapolate the individual aducanumab PET data from Weeks 26 to 54 and, also, to assign mean SUVr baseline value to each aducanumab dose group. Finally, the data from the Figure A2 were used to determine from which dose group the individual cumulative AUC at Week 26 from Figure A1 was most likely coming from.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Figure A1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



Source: Hang et al, 12th International Congress on Alzheimer's and Parkinson's Disease, Nice, March 18-22, 2015

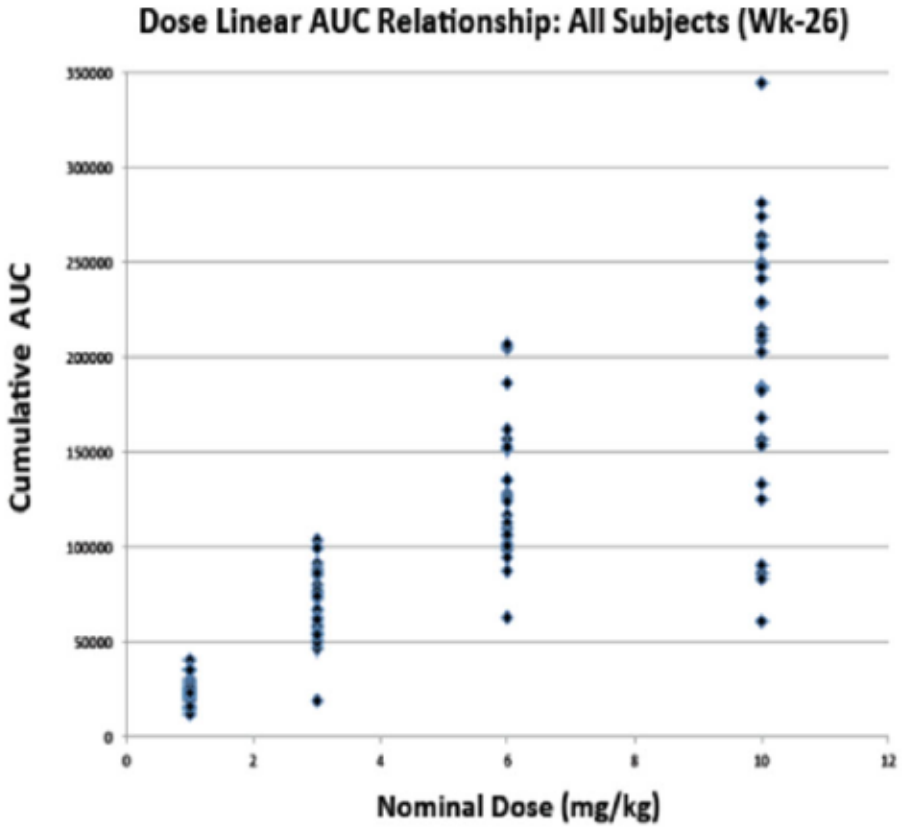
Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Table A2 Mean composite PET SUVr Data Observed in Aducanumab Phase 1b Trial (PRIME) Per Dose Group, Using the Whole Cerebellum as Reference Region

	Observed Mean Composite SUVr		
Dose group	Baseline	Week 26	Week 54
Placebo	1.45	1.42	1.42
1 (mg/kg)	1.45	1.395	1.346
3 (mg/kg)	1.471	1.365	1.3
6 (mg/kg)	1.44	1.288	-
10 (mg/kg)	1.434	1.223	1.152

Data derived from presented slide at ADPD conference.

Figure A2 Individual Dose-Exposure Relationship Observed in Aducanumab Phase 1b Trial (PRIME)



Subjects demonstrating low cumulative aducanumab exposures were primarily due to missed doses.

Source: Hang et al, 12th International Congress on Alzheimer's and Parkinson's Disease, Nice, March 18-22, 2015

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PKPD Model

Several structural PK-PD models were evaluated to best describe the link between exposure and SUVr PET. The tested models included a direct relationship, as well as an indirect relationship using an effect-compartment model to take into account a time delay for the concentrations in serum to reach the effect site.

Furthermore, several types of drug effect were tested, including a linear model, a power model, an Emax model, and a sigmoid Emax model.

No placebo models were evaluated because no peculiar placebo response was noticed over the observations period.

An additive error model was used for the residual variability. The baseline PET SUVr values were used as covariate in the model, but with an associated residual error of the same magnitude of the additive error model.

Interindividual variability was tested on the PK-PD parameters by assuming a log-normal distribution.

2.3.2 PK-PD Model Selection and Evaluation

Models were selected by visual inspection of basic goodness-of-fits plots, including, but not limited to, plots of the observed data versus population (PRED) and individual predictions (IPRED), plots of individual weighted residuals (IWRES) versus IPRED and the distribution of weighted residuals (WRES) over time. Relative standard errors (RSE) of the parameters were also compared to measure parameter precision. The NONMEM objective function value (OFV) was used to discriminate between nested models. This discrimination was based on a significance level of 0.05, which corresponds to a decrease in OFV of >3.84 (for one degree of freedom), as the difference in OFV is approximately χ^2-distributed [3].

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals derived from 1000 simulated data sets, using the final model and final parameter estimates, for each statistic (i.e., the median, the 5th and the 95th percentiles). Several VPCs were performed, either to test the appropriateness of the model when predicting the gantenerumab and aducanumab pooled dataset or to focus separately on the two compounds datasets. Furthermore, they were produced per level of exposure as well as per level of doses.

2.3.3 Computer Equipment

The analyses were performed in NONMEM Version 7.2, using FOCE INTERACTION (Beal and Sheiner 1992). Graphics and NONMEM datasets were created using Version 3.1.2 and/or the SAS System for Windows Version 9.3.

2.4 COVARIATE ANALYSIS

Only limited covariate information was available from the aducanumab data, and exploratory graphical analysis of individual posthoc parameters was conducted only for the following covariates: PET baseline values, compound type, gender, and doses.

3. RESULTS

3.1 DATA

The final PK-PD dataset combining aducanumab and gantenerumab data included 237 patients with a total of 693 PET SUVr observations.

3.2 POPULATION EXPOSURE SUVR PET MODEL

The relationship between exposure and the PET SUVr reduction time course was best described by using a power model combined with an effect compartment to account for the delay between exposure and PET response. The model equations are as follows:

$$PET(time) = Base * (1 - SLOP * (Conc_E(time))^{POW})$$

with $$\frac{\mathrm{dConc_E(time)}}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc(time)} - \mathrm{Conc_E(time)})$$

with Base the individual PET SUVr baseline value, $\mathrm{Conc_E}$ the predicted concentration at effect site, Conc the predicted concentration in serum, $\mathrm{Ke0}$ the rate constant for drug transfer from serum to effect compartment, and SLOP and POW the parameters driving the drug effect.

Parameter values are reported in Table A3.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Table A3 Estimated Population PK-PD Parameters

Parameters	Mean Value (RSE%)	Inter-individual variability (RSE%)
Ke0 (day^{-1})	$1.74x10^{-3}$ (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	-
POW (-)	0.716 (11%)	-
ADD_ERR	0.0659 (5%)	-

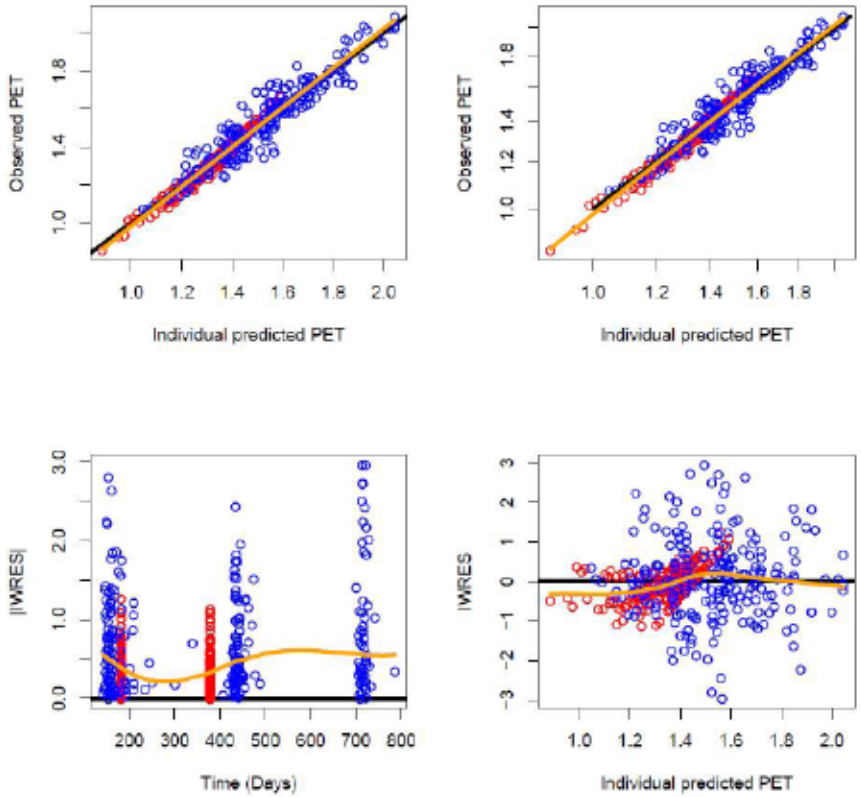
Inspection of the goodness-of-fit plots reported in Figure A3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures A5 to A7. The shaded areas indicate 90% confidence intervals (i.e., 5th and 95th percentiles) computed from simulations. The median and the 5th and 95th percentiles of the observed PK profiles are contained in their respective confidence intervals indicating that the final PK-PD model captures both the central tendency and the between subject variability of both gantenerumab and aducanumab pharmacodynamics in the target populations of patients with prodromal and mild Alzheimer's disease.

3.3 COVARIATE ANALYSIS

The exploratory graphical covariate analysis is reported on Figure A4. Although a small trend between PET baseline values and estimated individual Ke0, this graphical analysis did not reveal any relevant covariate relationships that would require further investigation.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

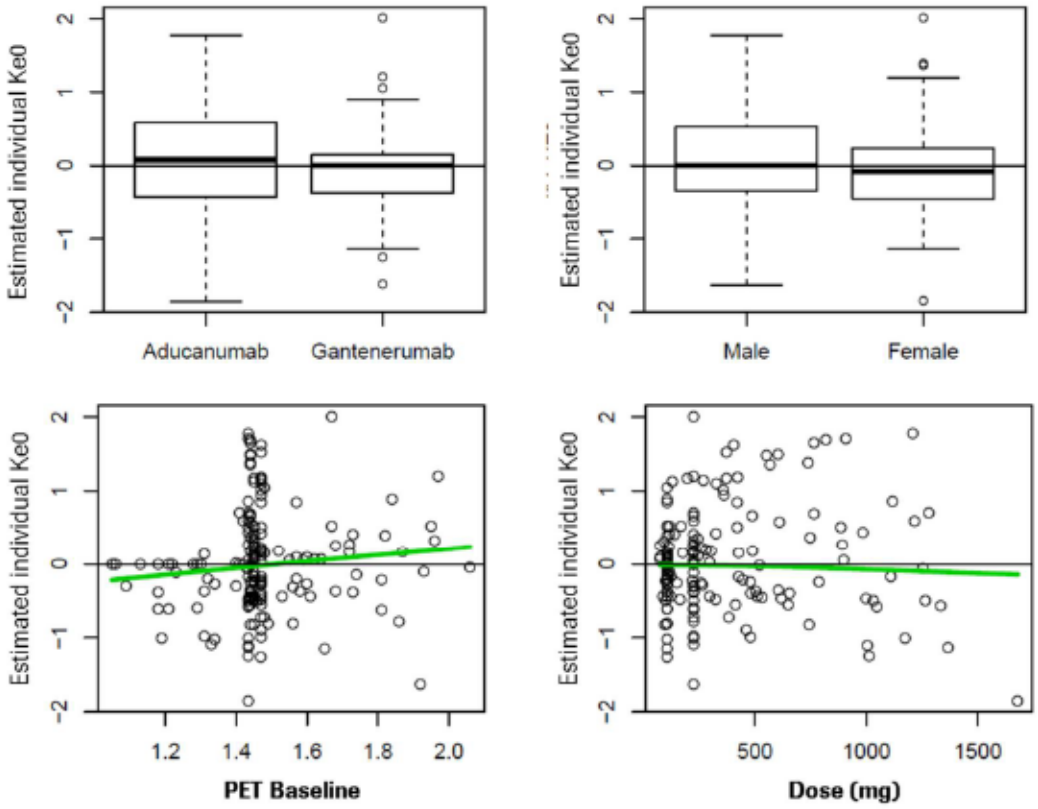
Figure A3 Goodness-of-Fit Plots for the Final PKPD Model



Note: The red dots represent aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smooth of the data.
WRES (IWRES) stands for population (individual) weighted residual values.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

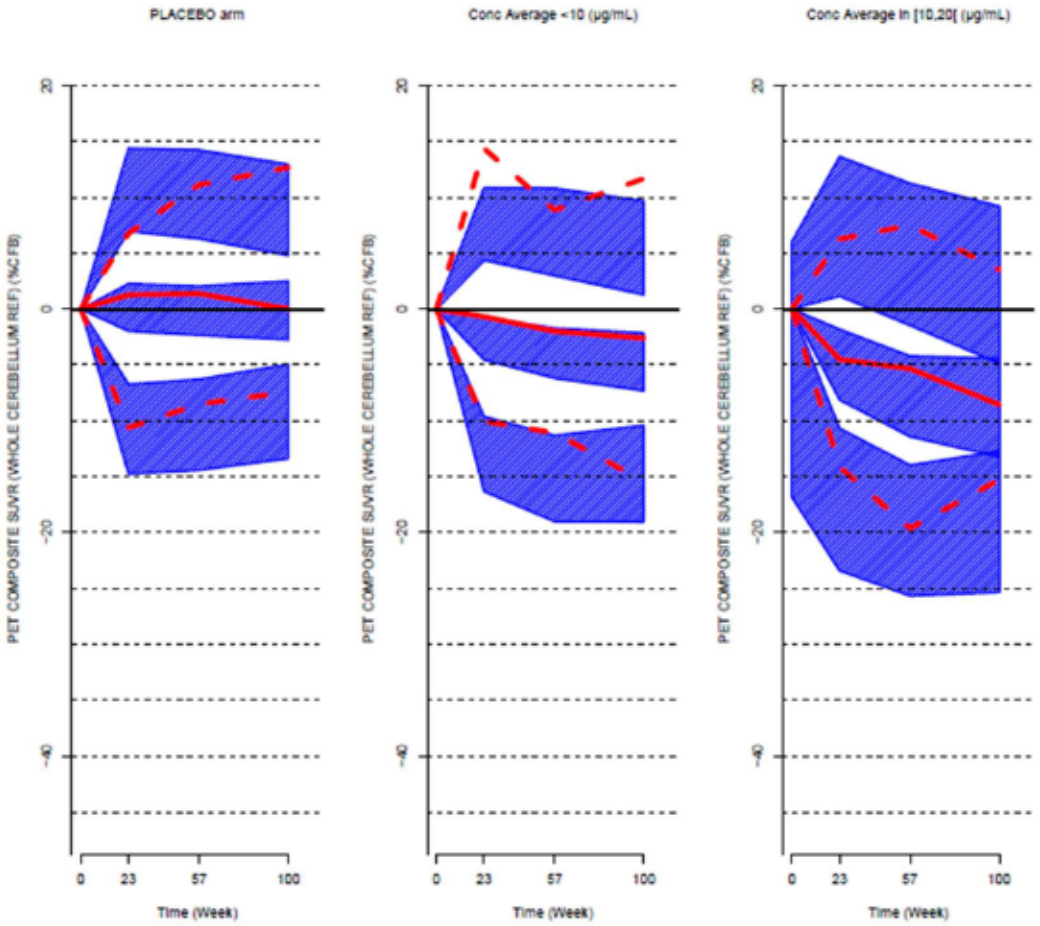
Figure A4 Exploratory Graphical Analysis of Covariates (Compound Type, Gender, PET Baseline Value, and Dose (mg) Value with Respect to Estimated Individual Ke0)



Note: Dose was investigated in mg, using a mean weight of 70 kg for doses from aducanumab trial (PRIME). The green line corresponds to a smooth of the data.

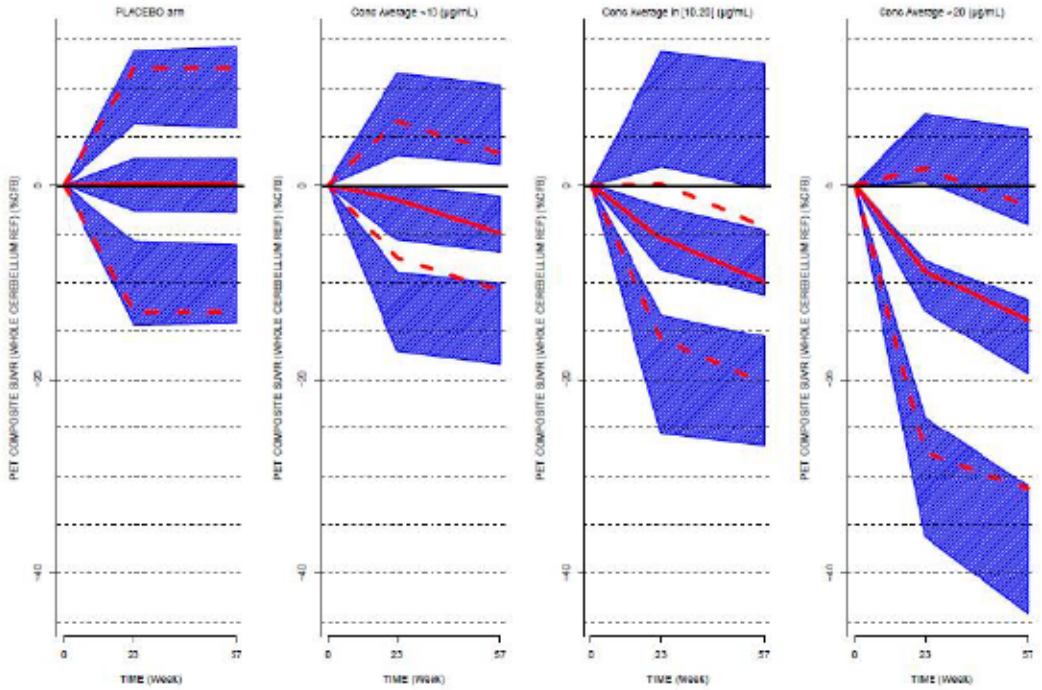
Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Figure A5 Visual Predictive Check of the PET Model Per Category of Serum-Concentrations Exposure for the Gantenerumab Trial (WN25203) Alone



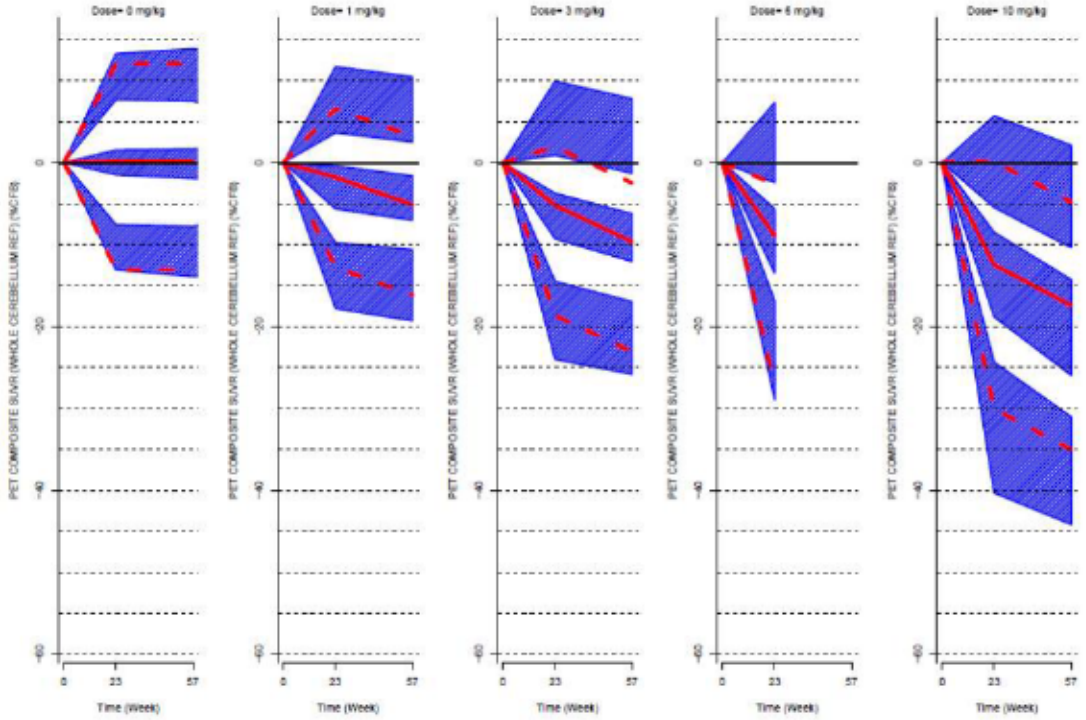
Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Figure A6 Visual Predictive Check of the PET Model Per Category of Serum-Concentrations Exposure for the Aducanumab Trial (PRIME) Alone



Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

Figure A7 Visual Predictive Check of the PET Model Per Category of Expected Dose Group for the Aducanumab Trial (PRIME) Alone



Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase 1b Study PRIME Data (cont.)

REFERENCES

Beal S. and Sheiner L. (Eds). NONMEM User Guides, NONMEM Project Group, University of California at San Francisco, San Francisco. 1992.