PROTOCOL

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR	[redacted], *MBBS, PhD*
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic date stamp below.

PROTOCOL AMENDMENT APPROVAL

Date and Time (UTC)	Title	Approver's Name
02-Aug-2021 12:03:00	Company Signatory	[redacted]

PROTOCOL HISTORY

Protocol	
Version	**Date Final**
4	*23 May 2020*
3	16 January 2020
2	11 February 2018
1	21 July 2017

PROTOCOL AMENDMENT, VERSION 5:
RATIONALE

The changes to the protocol, along with a rationale for each change, are summarized below:

- Section 1.3.5 Overall Benefit-Risk Summary has been updated to address the COVID-19 pandemic impact on the Benefit-Risk assessment for Study WN29922 as per the MHRA requirement
- Objectives and endpoints of the Double-Blind Treatment Period (Table 2) have been updated in the following manner:

– Corresponding endpoints for the 'exploratory efficacy' objective have been revised to remove 'in global outcome' as a criteria for the measurement of change from baseline to Week 116, which was added in error.

– The exploratory endpoint 'Time to clinically evident decline, defined as an increase of ≥ 2.0 in CDR-SOB subscore or ≥ 1 in at least four items of the FAQ' has been removed from Table 2, as it is not considered relevant anymore based on new available data.

– The exploratory endpoint 'Change from baseline to Week 116 measured by 'Function as assessed by the CDR function subscore" has been removed as it is no longer considered relevant based on new available data.

– The exploratory endpoint 'clinically evident decline as measured using the CDR' has been added to Table 2.

– The pharmacokinetic (PK) objective of the study has been changed to an exploratory PK objective to be consistent with the sparse PK sampling design and population modeling used to analyse the dose concentration–time data of gantenerumab. In addition, the protocol has been amended to enable early access PK, anti-drug antibodies (ADA) and pharmacodynamic (PD) biomarker samples. Early access will only be applied if there are sufficient sample data available to make an adequate assessment.

– The corresponding endpoints for the pharmacodynamic (PD) biomarker objective have been revised to clarify the duration of change as a measurement from baseline to Week 116 when assessing brain amyloid load, brain tau load and cerebral spinal fluid markers.

– The PD biomarker objective endpoint 'MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants ' has been reclassified as exploratory as it is no longer considered secondary based on new available data.

- Sections 3.1.1 and 4.1.3 have been updated to clarify that the open-label extension (OLE) of Study WN29922 is not applicable in countries that cannot run Study WN42171.
- Sections 4.1.2.7, 4.4.1, 4.7.2, and Appendix 1 have been revised to clarify the Medical Monitor's responsibility to review and support patient cohort management

and other protocol activities. Any reference to approval by the Medical Monitor with regards to medical decisions following enrollment has been removed from the protocol. The Principal Investigator (PI) may consult with the Medical Monitor/Sponsor for advice or clarification and may share risk factor information pertinent to the patient, but the medical decisions for the study participants are the responsibility of the PI.

- Section 4.1.3 has been amended to replace Week 104 with Week 116 (or Week 128, if applicable) which was omitted in the previous protocol amendment.
- Sections 4.6.3 and 4.6.4 have been amended to better clarify the order of assessments during the study visits
- Section 6.4.1 has been updated according to the estimand framework outlined in the ICH-E9 draft addendum with regards to the primary endpoint.
- Section 6.4.2 has been updated to remove the reference to time to event, which was included in error.
- Sections 6.4.4, 6.5 and 6.6 have been updated to clarify that a separate cut off may be necessary for PD biomarker, PK, and ADA samples to allow early access to PD biomarker samples and ensure expedient data analyses.
- Section 6.7.1 and 6.7.2 have been updated to include additional details surrounding the conduct of an interim analysis, should one be implemented.

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.

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PROTOCOL AMENDMENT ACCEPTANCE FORM

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted], *MBBS, PhD*
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 to the Sponsor or its designee. Please retain a signed copy of the form for your study files.

PROTOCOL SYNOPSIS

TITLE:	**A PHASE III, MULTICENTER, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP EFFICACY AND SAFETY STUDY OF GANTENERUMAB IN PATIENTS WITH EARLY (PRODROMAL TO MILD) ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN29922
VERSION NUMBER:	5
EUDRACT NUMBER:	2017-001364-38
IND NUMBER:	102,266
NCT NUMBER:	NCT03444870
TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase III
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease (AD). Specific objectives and corresponding endpoints for the study are outlined below for the double-blind treatment period and for the OLE period.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change in global outcome from baseline (Day 1) to Week 116 [a], as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function, as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a] in the following: • Clinically evident decline *as measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ=amyloid-β; AD=Alzheimer's disease; ADA=anti-drug antibody; ADAS-Cog11=Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13=Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E=amyloid-related imaging abnormalities–edema/effusion; ARIA-H=amyloid-related imaging abnormalities–hemosiderin deposition; CDR=Clinical Dementia Rating; CDR-GS=Clinical Dementia Rating global score; CDR-SOB=Clinical Dementia Rating–Sum of Boxes; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; QoL-AD=Quality of Life–Alzheimer's Disease; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including, but not limited to, total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory Pharmacokinetic Objective	***Corresponding Endpoint***
• *To characterize the PK profile of gantenerumab*	• *Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Study Design

Description of Study

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants: randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), apolipoprotein E (*APOE)* allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau positron emission tomography (PET) substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for mild cognitive impairment (MCI) due to AD). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the cerebral spinal fluid (CSF) tau to $A\beta_{42}$ ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the Free and Cued Selective Reminding Test (FCSRT) and Mini-Mental State Examination (MMSE). Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116.
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128. This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN29922 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data.

Participants will undergo brain magnetic resonance imaging (MRI) examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader. Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and quality-of-life (QoL) status. Blood samples for the assessment of PK samples, pharmacodynamic (PD) biomarkers, and ADA will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, amyloid-related imaging abnormalities–edema/effusion (ARIA-E) and ARIA–hemosiderin deposition (ARIA-H), injection site reactions (ISRs), adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded independent Data Monitoring Committee (iDMC).

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will use the OLE procedures described in this study. These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time

that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN29922 is not applicable in countries that cannot run Study WN42171.*

The study consists of three distinct periods:

- Screening (including an optional prescreening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

  OLE: All eligible participants will have the opportunity to enter an OLE study.

  – Eligible participants who enrolled early in the WN29922 study may start the OLE and will then transition to the open-label Study WN42171 (details will be provided in Protocol WN42171). Participants who terminated the WN29922 OLE early will be asked to come back for long-term follow-up visits.
  – If the WN42171 protocol is available and approved by local authorities, the remaining eligible participants will directly be enrolled in the open-label Study WN42171.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the National Medical Products Administration (NMPA) during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the Statistical Analysis Plan (SAP).

Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN29922: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in

participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the Study WN29922.

Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility.

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency, and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

Number of Patients

The planned enrollment specifies approximately 1016 participants.

Target Population

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee or Institutional Review Board)
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities,

temporal and spatial orientation, judgment and problem solving; emotional and psychological state; and can report any changes in the general health status

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the patient and participation in study procedures throughout the duration of the study

Every effort should be made to have same study partner participate throughout 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 [if applicable], clinical genotyping, and PET imaging [if applicable])

  The participant should be capable of completing assessments either alone or with the help of the study partner.
- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization
  - Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible
- 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
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry
- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $< 1\%$ per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state ($\geq$ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $< 1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

Exclusion Criteria

Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition
- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti–phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - $>$ 2 lacunar infarcts
  - Any territorial infarct $>$ 1 cm^3
  - Any white matter lesion that corresponds 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 $\geq$ 20 mm in any dimension

- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) 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 not compatible with MRI, 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

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the upper limit of normal (ULN) or total bilirubin $\geq 2\times$ ULN

Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

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

Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.
- Screening hemoglobin A_{1c} (HbA_{1C}) $>$ 8% (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent that is under evaluation 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 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).
- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

  Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for* any such use *it is recommended to* prospectively *seek* advice from the Medical Monitor and temporary study drug interruption *may be required*.
- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.
- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

  This may be based on, for example, the participant's sufficient education or work experience.
- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2 \times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured
  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer 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 excipients
- Any other severe or unstable medical condition 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 participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant'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: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period.
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment.
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures).
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable]* will stay in the double-blind treatment period until the finding is deemed resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

End of Study

The end of the study is defined as the date when the last patient, last visit occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

Length of Study

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN29922 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the participant will be kept in the WN29922 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

Investigational Medicinal Products

The investigational medicinal product (IMP) for this study is gantenerumab.

Test Product (Investigational Drug)

Gantenerumab or placebo will be administered by SC injection to all participants.

Double-Blind Treatment Period

Gantenerumab will be administered by SC injection to all patients randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose. Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

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

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

Open Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, administration will consist of one 0.8-mL and two 1.7-mL injections for the 120-mg dose or will consist of two 1.7-mL injections for the 255 mg dose and 510-mg dose. Injections will be administered subcutaneously to the abdomen.

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number).

For the OLE, the time window for dosing visits is $\pm$ 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Participants enrolled in the WN29922 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers 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.

Details about the PET substudies are described in separate protocols.

Statistical Methods

Primary Analysis

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12

weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB.*

  Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*

  Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):

  Treatment discontinued for non-study drug or condition–related reasons (NSDCR) reasons (e.g. purely administrative reason).
- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE. Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation of *the 12 week extension to the double-blind treatment period*. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits. To explore the robustness of MMRM results for the primary efficacy conclusions sensitivity analyses (e.g., using multiple imputation and pattern mixture models) will be performed. Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Determination of Sample Size

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have missed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

Interim Analyses

Optional Futility Analysis

The Sponsor may perform an interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with Study WN39658.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.

The iDMC may recommend to stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis. The failure criterion will be pre-specified in the iSAP.*

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis *which may include* efficacy*, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.*

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP.

Details of the interim analyses, including the decision to conduct the optional interim analysis, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility or efficacy thresholds) will be documented in the SAP, and the SAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
Aβ	amyloid-beta
AD	Alzheimer's disease
ADA	anti-drug antibody
ADAS-Cog11	Alzheimer's Disease Assessment Scale–Cognition, Subscale 11
ADAS-Cog13	Alzheimer's Disease Assessment Scale–Cognition, Subscale 13
ADCS-ADL	Alzheimer's Disease Cooperative Study Group–Activities of Daily Living
ADL	activities of daily living
APOE ε4	apolipoprotein E, allele ε4
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–hemosiderin deposition
AUC	area under the concentration–time curve
AUC_{inf}	area under the concentration–time curve from Time 0 to infinity
BOLD	blood oxygenation level-dependent
BGTS	Barkhof grand total score
CDR	Clinical Dementia Rating
CDR-GS	CDR global score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
C_{max}	maximum concentration
CNS	central nervous system
COA	clinical outcome assessment
CRO	contract research organization
CSF	cerebral spinal fluid
C-SSRS	Columbia–Suicide Severity Rating Scale
CT	computed tomography
CTAD	Clinical Trials in Alzheimer's Disease
DTI	diffusion tensor imaging
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQol-Five Dimensions questionnaire

Abbreviation	Definition
FA	fractional anisotropy
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FCSRT	Free and Cued Selective Reminding Test
FCSRT-IR	Free and Cued Selective Reminding Test–Immediate Recall
FDA	(U.S.) Food and Drug Administration
FLAIR	fluid-attenuated inversion recovery
GRE	gradient recalled echo
HbA_{1C}	hemoglobin A_{1c}
HIPAA	Health Insurance Portability and Accountability Act
HN	home nursing
ICE	intercurrent event
ICH	International Council on Harmonisation
iDMC	independent Data Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
ITT	intent to treat
IWG	International Working Group
IV	intravenous
IxRS	interactive voice or Web-based response system
LPLV	last patient, last visit
MAD	multiple-ascending dose
MCI	mild cognitive impairment
MMRM	mixed model repeated measure
MMSE	Mini-Mental State Examination
MRI	magnetic resonance imaging
NIA/AA	National Institute on Aging/Alzheimer's Association
NMPA	National Medical Products Administration
NPI-Q	Neuropsychiatric Inventory–Questionnaire
NSDCR	non-study drug or condition-related
OLE	open-label extension
PD	pharmacodynamic
PET	positron emission tomography
PK	pharmacokinetic

Abbreviation	Definition
PT	prothrombin time
p-tau	phosphorylated tau
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
Q2W	every 2 weeks
Q4W	every 4 weeks
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAD	single-ascending dose
SAP	Statistical Analysis Plan
SC	subcutaneous
SDCR	study drug or condition-related
SOB	Sum of Boxes
SUVr	standardized uptake value ratio
t-tau	total tau
ULN	upper limit of normal
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview–Alzheimer’s Disease

1. BACKGROUND

1.1 BACKGROUND ON ALZHEIMER'S DISEASE

The World Health Organization estimates that around 50 million people worldwide are diagnosed with dementia and that there are 10 million new cases every year. The total number of people with dementia is estimated to reach 82 million in 2030 and will more than triple by 2050 to 152 million. AD is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2017). The prevalence of AD increases with age, with a global prevalence of 5%–8% in people 60 years and older. 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.

There is great inter-individual variability in AD progression with survival dependent on many factors, including age at onset. In general, the clinical picture evolves from "predementia" or "prodromal AD" to mild, moderate, and then severe AD. At the early stage of AD, a slight impairment of memory, language, and visuospatial function can be observed. As AD advances, patients become progressively impaired and the burden on caregivers significantly increases. The median survival time following a diagnosis of AD strongly depends on the patient's age at diagnosis and ranges from 8.3 years for persons diagnosed with AD at 65 years old to 3.4 years for those 90 years old (Brookmeyer et al. 2002). On average, individuals live 3–9 years after diagnosis (Helzner et al. 2008) and some survive as long as 20 years.

It is well recognized that in comparison to other therapeutic domains, there is a real unmet medical need in AD therapy (Gauthier et al. 2016). To date, only five medications have received marketing approval to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEi) and N-methyl-d-aspartate receptor antagonists. These approved drugs are recognized to temporarily improve some clinical symptoms of AD in some patients but do not modify progression of the disease (Cummings et al. 2016). Recent efforts have mostly focused on therapies targeting amyloid (Bachurin et al. 2017) as these offer the most compelling therapeutic targets (Graham et al., 2017). These therapies are based on the amyloid hypothesis that posits amyloid-β (Aβ) accumulation as the primary factor driving Aβ pathogenesis (Selkoe 1991; Hardy and Selkoe 2002; Selkoe and Hardy 2016). This Aβ accumulation in the brain begins well before the development of clinical dementia in AD and causes a series of downstream events leading to synaptic dysfunction, inflammation, neurodegeneration, and clinical symptoms. For these reasons, treatments that prevent, slow, or decrease the accumulation of brain Aβ are being tested as therapeutic agents in AD.

Preclinical evidence has suggested that monoclonal Aβ antibodies may be able to remove and reduce deposition of Aβ aggregates from the brain. In transgenic animal models of AD, vaccination with Aβ or passive immunization with anti–Aβ antibodies resulted in decreased amyloidosis and in improvement of memory function in some transgenic models cognitive function (Janus et al. 2000). Accumulating clinical evidence

also supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the CSF (Roche Research Report No. 1066251). In a Phase I study, reduction of deposited amyloid as shown on brain amyloid PET imaging was associated with a time and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the neurological changes associated with AD develop decades before clinical symptoms emerge, it is thought that earlier intervention may be more effective in arresting or delaying disease progression (Sevigny et al. 2016). Consequently, therapies targeting this process have the potential to significantly alter the progression of the disease. Gantenerumab, a fully human monoclonal antibody targeting aggregated forms of Aβ-like Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (or RO4909832) is a fully human anti−Aβ peptide antibody developed by in vitro selection utilizing aggregated Aβ and in vitro maturation within a complete human Igγ, subclass-1 framework (IgG1). Gantenerumab recognizes a conformational epitope of Aβ present in aggregated Aβ and that is demonstrated for both major species of Aβ that is, $Aβ_{1-40}$ and $Aβ_{1-42}$. Gantenerumab has a molecular mass of 146.3 kDa. In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6−1.2 nM). Based on additional in vitro studies and studies in animal models, the pharmacologic profile suggests that in humans, gantenerumab may prevent, inhibit, and reduce accumulation of Aβ, which is believed to play an important role in the pathogenesis of AD.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary−K1 mammalian cell line and subsequent purification of the antibody. The gantenerumab drug substance manufacturing was optimized during development, leading to several manufacturing processes (G1, G2, and G3). Recently, the gantenerumab manufacturing process was further optimized from G3 to G4 to improve process robustness and increase overall process yield. Drug material manufactured by G4 process is used in Phase III clinical trials (e.g., Study WN29922). 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).

Refer to the gantenerumab Investigator's Brochure for details on nonclinical and clinical studies.

1.2.1 Nonclinical Studies

1.2.1.1 Nonclinical Pharmacology

The binding characteristics of gantenerumab were engineered to achieve specific and highly sensitive recognition of the assembly structure of aggregated human $Aβ_{1-42}$ and $Aβ_{1-40}$ peptides, which are major components in Aβ plaques. Specificity was

demonstrated ex vivo for genuine human Aβ plaques in AD brain slices. The minimum effective concentration for staining of human Aβ plaques is 10 ng/mL (0.07 nM).

Gantenerumab showed a concentration-dependent increase in cellular phagocytosis of human Aβ plaques by human primary cells like microglia and differentiated macrophages in a brain-slice phagocytosis assay. The measured minimal effective concentration of 10 ng/mL (0.07 nM) is consistent with the observed efficacy for human Aβ plaque binding.

In single-dose and multiple-dose studies, effective brain penetration and binding to Aβ plaques in vivo were demonstrated in various models of AD-related amyloidosis, such as the PS2APP transgenic mouse model. Gantenerumab showed significant and accumulative binding to Aβ plaques. The data indicate that there is no requirement for continuous high peripheral levels to achieve a sustained binding of gantenerumab to amyloid plaques.

The plaque binding of gantenerumab from several manufacturing processes has been evaluated. The degree of plaque binding for gantenerumab manufactured by the G1 and G2 processes was investigated by semi-quantitative fluorescence imaging and was comparable in a 2-week IV safety study in PS2APP transgenic mice at doses of 0, 2, 10, and 40 mg/kg every 3 days.

An additional study, which compared the plaque binding of gantenerumab from the G3 and G4 manufacturing processes following single IV administration to PS2APP transgenic mice at a dose level of 40 mg/kg and assessed by semi-quantitative fluorescence imaging after 7 days, indicated slightly increased target engagement of the G4 material consistent with observed differences in exposure (see Section 1.2.1.2).

Chronic treatment with gantenerumab showed significant efficacy by halting progression of amyloidosis in transgenic PS2APP, APP_{London}, and tau PS2APP mouse models of AD. Amyloid reduction was evident by prevention of new plaque formation and removal of preexisting amyloid plaques by engaging microglia cells.

1.2.1.2 Nonclinical Pharmacokinetics and Metabolism

The pharmacokinetics of gantenerumab were studied in mice, rats, and cynomolgus monkeys following IV administration. Gantenerumab pharmacokinetics were characterized by a rapid initial decrease in plasma levels during the first 24 hours, followed by a long half-life, ranging from 4 to 13 days in all species. Overall, the studies demonstrate that gantenerumab has PK properties similar to other IgGs.

The pharmacokinetics of gantenerumab were also studied following SC administration in cynomolgus monkeys and mice. In cynomolgus monkeys, maximum plasma levels were reached after 3 days. The average bioavailability was estimated at 76%.

Gantenerumab was shown to penetrate the brain in both the monkey and mouse. Brain penetration in the monkey was evident from analysis of CSF samples. The CSF to plasma ratios ranged from 0.006% to 0.018%. Penetration and binding to $A\beta_{1-42}$ plaques in the mouse brain were evident from immunostaining for gantenerumab of brain sections obtained from PS2APP mice dosed with gantenerumab.

Rat PK studies have been conducted to compare the pharmacokinetics of gantenerumab derived from different manufacturing processes (G1, G2, G3, and G4).

Following IV administration to rats, the pharmacokinetics of the G1 and G2 materials were similar. The area under the concentration–time curve (AUC) of the G2 material was slightly lower and accounted for about 80% of the of the G1 material. Although standard bioequivalence criteria for AUC were not met, the observed difference in AUC was not considered to have an impact on the use of the G2 material in further clinical development as the difference in AUC is small. The average terminal half-life of both materials was comparable (8.0 and 8.8 days for the G1 and G2 materials, respectively).

A study comparing the pharmacokinetics of gantenerumab derived from the G3 and G4 manufacturing processes showed that the AUC of G3 material (used in the ongoing Phase III OLE Studies WN25203 and WN28745) was lower compared with the G4 material that will be used in Study WN29922 (mean±SD: 932±196 and 1270±187 (μg• hr/mL)/(mg/kg), respectively. The average terminal half-life of both materials was similar (11.5 and 12.3 days for G3 and G4 materials, respectively).

1.2.1.3 Toxicology and Safety Pharmacology

Potential adverse effects in relation to the presence and destruction of $A\beta_{1-42}$ plaques were assessed in PS2APP transgenic mice that were treated with up to 375 mg/kg/wk of IV gantenerumab for up to 26 weeks. No evidence of inflammatory reaction in general or other adverse effects were observed in these studies. Decreases in neutrophils and protein (albumin) that were not considered adverse were seen in mice. As a compensatory response, myeloid hyperplasia in the bone marrow was inconsistently detected in some animals. The reason for the low neutrophil counts is unclear but may be a mouse-specific effect of gantenerumab on neutrophils. Indeed, no such finding was observed in long-term nonclinical (murine and monkey) and clinical studies, and there have been no symptoms indicating immunosuppression in either species.

In cynomolgus monkeys, gantenerumab was well tolerated in repeat-dose IV toxicity studies of 13 and 26 weeks in duration (3, 10, and 20 mg/kg) and in SC toxicity studies of 13 weeks in duration (20 mg/kg) and 39 weeks in duration (up to 375 mg/kg). In the 26-week toxicity study, in which gantenerumab was administered once weekly, one male monkey in Group 2 (3 mg/kg) was found dead 24 hours after receiving the 26th dose (Day 177). The death was not considered to be related to gantenerumab treatment but rather to a bacterial infection detected on histopathology. There was no

treatment-related effect on hematologic parameters (i.e., neutrophil counts) in studies in cynomolgus monkeys.

In the absence of any adverse treatment-related effect in the 39-week toxicity study, a no-observed-adverse-effect level of 375 mg/kg/wk was established, which correlated with a mean maximum concentration (C_{max}) of 2535 μg/mL (male and female animals combined) and a mean area under the concentration–time curve from Time 0 to 168 hours ($AUC_{0-168hr}$) of 386,000 μg • hr/mL (male and female animals combined).

Reproductive toxicity studies in transgenic PS2APP mice did not reveal an effect of gantenerumab on fertility, embryo–fetal, or post-natal development.

1.2.2 Clinical Studies

Gantenerumab has been investigated in 10 completed Phase I clinical studies: three single-ascending dose (SAD) studies (BN18726, JP22474, and BP30042) of healthy volunteers and patients with mild to moderate AD, two multiple-ascending dose (MAD) studies (NN19866 and JP22431) of patients with mild to moderate AD, and three bioavailability studies of healthy subjects (one comparing the IV and SC formulations of gantenerumab [Study WP22461], two comparing lyophilized and high-concentration liquid formulations of gantenerumab [Studies WP27951 and BP29113]). In addition, a tolerability study comparing the pain between faster and slower SC administrations of gantenerumab has been completed (Study WP39322).

In order to assess suitability of the G4 material for future Phase III studies, an extended analytical comparability program was conducted followed by the nonclinical studies. Since differences were observed in AUC, a human relative bioavailability study (WP40052) comparing G3 and G4 gantenerumab after SC administration has also been conducted.

A total of 543 subjects have participated in the Phase I studies; of these participants, 406 healthy volunteers and 101 patients with AD have received gantenerumab.
Two Phase III studies designed to examine efficacy and safety of gantenerumab in patients with prodromal AD (Study WN25203) and mild AD (Study WN28745) have been converted to OLE studies. The OLE studies examining the safety and tolerability of higher doses of gantenerumab in prodromal AD (Study WN25203) and mild AD (Study WN28745) are ongoing.

Results of relevant studies are summarized below. Refer to the Gantenerumab Investigator's Brochure for further information.

In addition, gantenerumab is being investigated in the Dominantly Inherited Alzheimer Network Trial, a Phase II/III study sponsored by the Washington University School of Medicine, examining the safety, tolerability, biomarker status, and efficacy of gantenerumab (as measured by cognition) in patients who are known to have an AD-causing mutation and are therefore at risk for developing AD dementia.

1.2.2.1 Study NN19866

In the MAD study (NN19866), a total of 60 patients (34 males and 26 females) diagnosed with mild to moderate probable AD received multiple IV doses of gantenerumab (doses ranging from 6 mg to 20 mg, 60 mg, and 200 mg) or placebo every 4 weeks (Q4W) for up to 7 months. Owing to amyloid-related imaging abnormalities (ARIAs), or ARIAs of “vasogenic edema” (ARIA-E) and of “hemosiderosis or microbleeds” (ARIA-H), on brain magnetic resonance imaging (MRI) scans that occurred in some patients after two to four doses of 200 mg of gantenerumab in Cohort 4 (200 mg IV Q4W gantenerumab [equivalent to 330 mg SC Q4W] or placebo), it was decided to terminate dosing for all patients on 9 June 2008. The findings resolved spontaneously within 1–4 months after discontinuation of gantenerumab and no patient required treatment.

1.2.2.1.1 Study NN19866: Pharmacodynamic Results in the NN19866-PET Substudy

In a PET substudy of Study NN19866 (NN19866-PET), the effects of gantenerumab on amyloid load in the brain (defined as standardized uptake value ratio [SUVr] of a cortical composite volume of interest over mean cerebellum gray and using ^{11}C-PiB PET) were evaluated in 18 patients (4 in the placebo group, 8 in the 60-mg IV gantenerumab dose group, and 6 in the 200-mg IV gantenerumab dose group) after 6 months. A mean decrease of 14.9% from baseline was observed in the 200-mg gantenerumab dose group, while an increase was seen in the placebo group (mean, 20.9%), with relative stability compared with baseline in the 60-mg group (mean, 5.3%) (Ostrowitzki et al. 2012).

1.2.2.2 Study WN25203

Based on the results from Study NN19866 and from a relative bioavailability Study WP27951, the doses of 105 mg SC Q4W (equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were selected for Study WN25203.
Study WN25203 was initially designed as a Phase III, randomized, double-blind, placebo-controlled, parallel-group, multicenter study to evaluate the safety and efficacy of 105 mg and 225 mg of gantenerumab administered subcutaneously Q4W in prodromal AD after 2 years of treatment. Randomization was based on apolipoprotein E, allele ε4 (*APOE* ε4) status. Selection of gantenerumab doses was largely driven with the objective of reducing risk of MRI findings (in the context of the clinical understanding of ARIAs at the time of study design) and by pharmacodynamic (PD) results in the MAD Study NN19866. Study WN25203 enrolled 799 patients, and 797 patients were treated (the safety-evaluable population). Following a planned interim futility analysis when

approximately 50% of patients had completed 2 years of treatment, the study was declared futile and dosing with the originally selected doses (105 mg and 225 mg) was suspended in December 2014. The mean duration of double-blind treatment was 1.73 years.

Safety analyses confirmed ARIAs and injection-site reactions (ISRs) (associated with SC administration) as identified risks of gantenerumab (see Section 1.2.3 for more details). Approximately 90% of patients experienced at least one adverse event, with the incidence comparable between treatment arms. The incidence of serious adverse events was 19.5%, 17.3%, and 16.9% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (Ostrowitzki et al. 2017).

Subsequently, the trial has been converted into an OLE study evaluating doses of up to 1200 mg (see Section 1.3.1).

1.2.2.3 Study WN28745

Study WN28745 was initially designed as a Phase III, 2-year, double-blind, placebo-controlled, efficacy, and safety study of gantenerumab in approximately 1000 patients with mild AD. Patients randomized to receive gantenerumab were to follow a slow titration scheme independent of *APOE*-ε4 genotype, starting at 105 mg of SC gantenerumab Q4W for the first 24 weeks, with progression to 225 mg, based on acceptable results of the control MRI scan. Enrollment into the double-blind phase of the study was stopped in November 2015 because of the futility of Study WN25203. When Study WN28745 was stopped, 389 patients had been enrolled and 387 patients had been treated. There were 108 patients who were also enrolled in a PET substudy of brain amyloid imaging (Study WN28745-PET).

In the double-blind phase of Study WN28745, gantenerumab was found to be safe and well tolerated by patients with mild AD. Adverse events were reported for 80.5% of patients in the placebo group and for 82.8% of patients in the gantenerumab groups, respectively. The most commonly reported adverse events across all treatment groups included fall (8.5%), nasopharyngitis (7.5%), headache (7.0%), dizziness (5.7%), ARIA-E (5.4%), and back pain (5.4%). ISRs, ARIA-E, and ARIA-H were reported more commonly in patients in the gantenerumab group than in the placebo group (ISR: 8.3% vs. 1.0%; ARIA-E: 9.4% vs. 1.5%; ARIA-H: 6.3% vs. 4.1%).

Following the WN25203 futility analysis, the study was converted to an OLE study, evaluating the safety and tolerability of gantenerumab at higher doses (up to 1200 mg).

1.2.2.4 OLE Studies WN25203 and WN28745

Additional analyses of Study WN25203 results indicated that higher doses of gantenerumab may achieve clinically relevant effects on cognition and function (see Section 1.3.1). Thus, both Studies WN25203 and WN28745 were converted to OLE

studies to provide participants, including those in the placebo group, the opportunity for treatment with higher doses of gantenerumab expected to have a clinically meaningful effect. Doses up to 1200 mg SC Q4W of G3 gantenerumab are being tested, using dosing regimens designed to minimize the risk of ARIAs and taking into account the *APOE* genotype and the previous double-blind treatment and dose.

As of 1 May 2019, 383 patients had been enrolled in the OLE Studies WN25203 and WN28745, with 363 patients exposed to G3 gantenerumab doses higher than 225 mg (i.e., more than the highest repeat dose previously tested in AD patients) and 309 patients having reached the OLE target 1200-mg dose. ISRs and ARIAs remain the identified risks for gantenerumab. Continuous monitoring of safety data and MRI findings by the Sponsor has not identified any new safety signal in these ongoing studies. These OLE studies will be ending in 2020, and patients will be provided with an option to enroll in an open-label, rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (WN41874).

1.2.2.5 Study WP40052

A total of 114 healthy male and female subjects received a single dose of 600 mg of gantenerumab high concentration, liquid formulation (containing gantenerumab manufactured by either G3 or G4 process, N = 57 in each treatment group). The results showed that the plasma exposure in terms of area under the concentration–time curve from Time 0 to infinity (AUC_{inf}) was approximately 1.18 fold higher after SC administration of material manufactured by G4 process compared with material manufactured by G3 process, whereas C_{max} was similar (1.05 fold higher after administration of G4 material). Single-dose SC administration of 600 mg of gantenerumab as G3 or G4 material was safe and well tolerated.

Refer to the Gantenerumab Investigator's Brochure for details on clinical studies.

1.2.3 Safety Overview

Nonclinical characterization of gantenerumab did not show any relevant safety findings. To date, ARIAs and ISRs are the identified risks for gantenerumab. No differences between active and placebo groups have been observed in laboratory parameters, physical and neurological examinations, vital signs, or electrocardiogram (ECG) parameters.

Amyloid-Related Imaging Abnormalities

In the double-blind phase of Study WN25203 (prodromal AD), ARIA events were time, dose, and *APOE* ε4 allele status dependent. The incidence of ARIA-E was 0.8% in the placebo, 6.6% in the 105-mg gantenerumab, and 13.5% in the 225-mg gantenerumab groups. For ARIA-H, the incidence was 13.2% in the placebo, and 22.9% and 16.2% in the 105-mg and 225-mg gantenerumab treatment groups, respectively. The rates of new ARIA-E were highest between 3 and 6 months of treatment (3.8% and 7.5% in the 105-mg and 225-mg gantenerumab groups, respectively) and decreased substantially after

the first year of treatment (incidence of up to 2.3% in the 225-mg gantenerumab group in approximately 2 years). The median MRI Barkhof grand total score (BGTS) (Barkhof et al. 2013) of these findings was 3. Most ARIA events were asymptomatic and did not lead to clinically significant consequences. A total of 5 patients (1.8%) from the 105-mg gantenerumab arm and 6 patients (2.3%) from the 225-mg gantenerumab arm experienced symptoms related to ARIA findings; the most commonly reported symptom was headache (5 patients). Other symptoms reported with ARIA-E included visual disturbances (left eye diplopia and upper left quadrantanopia), focal seizure (dysarthria/aphasia that lasted for 10 minutes), anxiety, hyperreflexia, confusional state, disturbance in attention, cognitive disorder, malaise, and dizziness. Symptomatic ARIAs were of mild severity and were non-serious except for one serious adverse event of focal seizure.

Following the futility analysis for Study WN25203, treatment in the double-blind phase was discontinued in July 2017 (median double-blind treatment duration: 68 weeks) and consenting patients transitioned into OLE.

In the double-blind phase of Study WN28745, the frequency of ARIA-E was 1.5% and 11.5% in the placebo and gantenerumab groups, respectively. The frequency of ARIA-H was 11.8% and 15.1% in the placebo and gantenerumab groups, respectively. The median BGTS of ARIA-E was 3. Most ARIAs were asymptomatic and did not lead to clinically significant consequences. Two patients reported CNS adverse events as symptoms of ARIAs: one patient (0.5%) in the placebo group reported irritability that was mild in intensity and non-serious, and one patient (0.5%) in the gantenerumab group reported headache that was moderate in intensity and non-serious.

The WN25203 and WN28745 OLE studies are ongoing and consequently, data are still accruing. As of 1 May 2019, all 154 patients dosed with gantenerumab in the WN25203 OLE study had a post-baseline MRI scan. Of 154 patients, 47 (30.5%) had new ARIA-E (median maximum BGTS of 7.0), and 14 of 154 patients (9.1%) had new ARIA-H without ARIA-E. The majority of ARIA-E findings were asymptomatic, with 11 out of 47 patients with new ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, and did not require permanent cessation of study treatment. Most symptomatic ARIA-E cases resolved with protocol-defined ARIA management rules. In 3 of the 11 patients with ARIA-E MRI findings who reported associated CNS adverse events, the events were reported as serious (confusional state, seizure, and epilepsy).

As of 1 May 2019, 219 of 225 patients dosed with gantenerumab in the WN28745 OLE study had a post-baseline MRI scan. Seventy-one of 219 patients (32.4%) had new ARIA-E (median maximum BGTS of 9.0), and 24 of 219 patients (11.0%) had ARIA-H without ARIA-E. The majority of ARIA-E events were asymptomatic, with 18 of 71 patients with ARIA-E MRI findings reporting associated CNS adverse events. The CNS adverse events were mostly mild to moderate in intensity, non-serious, did not

require permanent cessation of study treatment, and resolved with protocol-defined ARIA management rules. In 4 of the 18 patients with symptomatic ARIA-E, the events were reported as serious (ischemic stroke, generalized tonic-clonic seizure, epilepsy, and hemiplegia).

Overall, gantenerumab uptitration is associated with a lower rate of ARIA than the predicted rate for fixed dose, and the ARIA-E incidence observed in the OLEs has been in the expected range and in alignment with the ARIA-E PK/PD model. ARIAs are clinically manageable by protocol-defined MRI monitoring and dose intervention algorithms.

Injection-Site Reactions

In the double-blind phase of Study WN25203, the incidence of ISRs was 4.5%, 18.8%, and 23.1% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively. All ISRs were non-serious, and the majority were mild in intensity and resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, and rash. Two patients (0.3%) discontinued study treatment due to ISR.

In the double-blind phase of Study WN28745, the incidence of ISRs was 1.0% and 9.4% in the placebo and gantenerumab groups, respectively. All ISRs were non-serious and mild in intensity; the vast majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, pruritus, hemorrhage, and rash. No patients discontinued study treatment due to ISR.

As of 1 May 2019, ISRs have been reported in 56 of 154 (36.4%) patients dosed with gantenerumab in the WN25203 OLE study, and 45 of 154 (29.2%) patients have had recurrent ISRs. All ISRs were non-serious and mild, and the majority resolved without treatment. Overall, 3 of 56 (5.4%) patients who had an ISR received treatment, which included topical steroids and antihistamines.

As of 1 May 2019, ISRs have been reported in 86 of 225 (38.2%) patients treated with gantenerumab in the WN28745 OLE study and 58 of 225 (25.8%) patients have had recurrent ISRs. All ISRs were non-serious, with the majority being mild and resolving without treatment. Overall, 9 of 86 (10.5%) patients who had an ISR received treatment, which included topical steroids and antihistamines. One patient (0.3%) experienced a severe event (injection-site pain after receiving a 600 mg dose via a pump, resulting in dose modification [i.e., uptitration was delayed]); this ISR resolved within 24 hours.

The Sponsor performs regular reviews of OLE Studies WN25203 and WN28745 data and, to date, has not identified any new or unexpected safety findings.

For safety data from all studies, refer to the Gantenerumab Investigator’s Brochure.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

Currently, approved therapies for AD focus on symptomatic approaches that target synaptic function and cognitive enhancement (Cummings 2004). However, the amyloid hypothesis suggests that overproduction of Aβ or failure to effectively clear this peptide contributes to AD (Selkoe and Hardy 2016) and that accumulation of Aβ peptides is one factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Despite compelling results in AD animal models (Wisniewski and Goñi 2014), clinical success with passive immunization targeting brain amyloid in global Phase III trials remains an unachieved goal. It has been suggested that lack of sufficient target engagement of anti-amyloid antibodies has been a factor in the failure of these Phase III studies (Cummings et al. 2016). An important advancement for therapies targeting aggregated amyloid was provided based on data from the Phase Ib PRIME study of aducanumab (Biogen) (Sevigny et al. 2016).

Aducanumab is a fully human IgG1 monoclonal antibody with similar PK and PD properties as gantenerumab that binds to aggregated target fibrillary and oligomeric forms of Aβ through microglia-mediated clearance of amyloid plaques (Sevigny et al. 2016). The results from the PRIME study showed that monthly IV injections of aducanumab for 1 year led to a dose- and time-dependent reduction of amyloid plaques in the brain. In addition, in patients with early (prodromal to mild) AD, a slowing of clinical decline, as measured on the Clinical Dementia Rating–Sum of Boxes (CDR-SOB) and MMSE scores, has also been observed providing support to the hypothesis that Aβ plaque reduction confers clinical benefit.

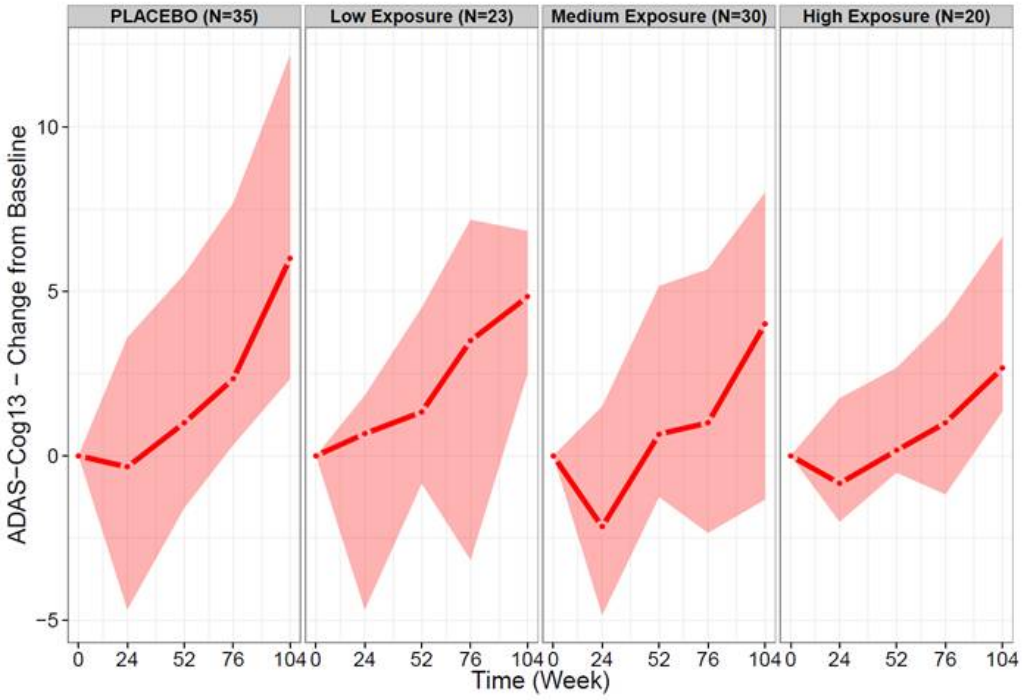
1.3.1 Study Rationale

The results of the preplanned futility analysis of data from approximately 300 patients in Study WN25203 revealed the low likelihood for trial success with the original doses studied. Indeed, no significant differences were observed on any cognitive or functional measures (i.e., CDR-SOB, MMSE, Alzheimer Disease Assessment Scale–Cognition, Subscale 13 [ADAS-Cog13], and Functional Activities Questionnaire [FAQ]) or in a subgroup analysis of baseline characteristics (demographics, cognitive, CSF biomarkers, disease severity, or *APOE* ε4 allele status). Additional post-hoc analyses indicated that the overall rate of clinical decline was lower than expected for this study population (and with higher-than expected proportion of “slow progressors”) and strongly suggested that the doses studied in Study WN25203 (105 and 225 mg) were subtherapeutic and that a higher gantenerumab dose may have a clinically relevant effect (Ostrowitzki et al. 2017).

Results of the post-hoc analyses of patients who were predicted to be progressors using a model derived from the Alzheimer’s Disease Neuroimaging Initiative data

(Delor et al. 2013) showed a drug concentration-dependent effect on clinical decline present for the ADAS-Cog13, MMSE, and Cambridge Neuropsychological Test Automated Battery results. Figure 1 displays the effects on increasing plasma gantenerumab concentrations (three concentration groups) on ADAS-Cog13 decline over the 2-year study. Greater concentrations of gantenerumab were associated with less clinical decline.

Figure 1 ADAS-Cog13 Treatment Response by Plasma Concentration: Two-Year Completing Fast Progressors in Study WN25203

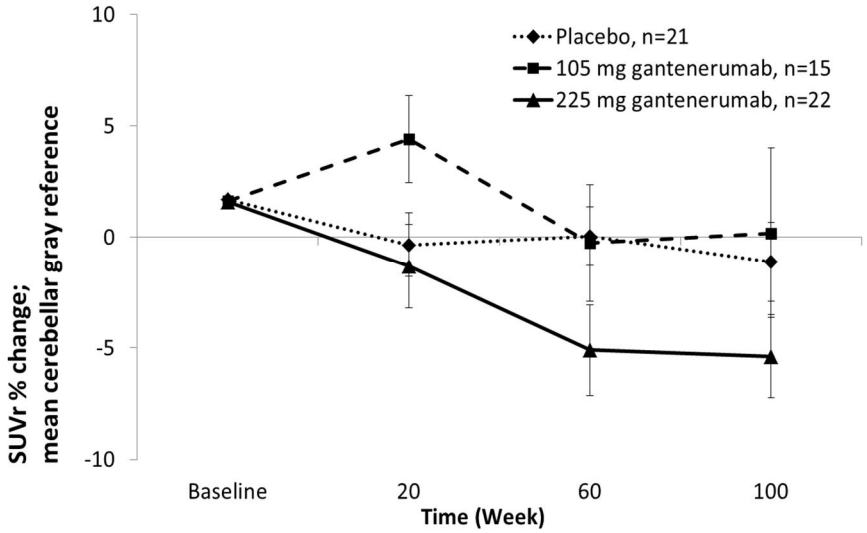


ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13.
Notes: low exposure = 1.48–5 μg/mL; medium exposure = 5–10 μg/mL;
high exposure = 10–26.68 μg/mL. Line = median; shaded = 50% observations.

Furthermore, a PET substudy of Study WN25203 using [^{18}F] florbetapir confirmed a reduction in brain amyloid in gantenerumab-treated patients in a larger, less-impaired patient sample compared with Study NN19866, which had also demonstrated reduced accumulation of brain amyloid. Time-dependent reductions in SUVr were observed in patients treated with 225 mg of gantenerumab compared with placebo using the composite cortical SUVr and reference region of mean cerebellar gray. Week 100 results showed the mean percent change from baseline in SUVr was −1.09%, 0.72%, and −4.82% in the placebo, 105-mg gantenerumab, and 225-mg gantenerumab groups, respectively (see Figure 2). A small number of patients (n = 8) continued to receive 225 mg of gantenerumab for approximately 3 years (Week 156). Analysis suggested that the effect on SUVr reduction was continuous over time because SUVr reductions

observed with the 225-mg dose of gantenerumab relative to placebo increased with the duration of long-term exposure, suggesting a sustained effect with continued exposure.

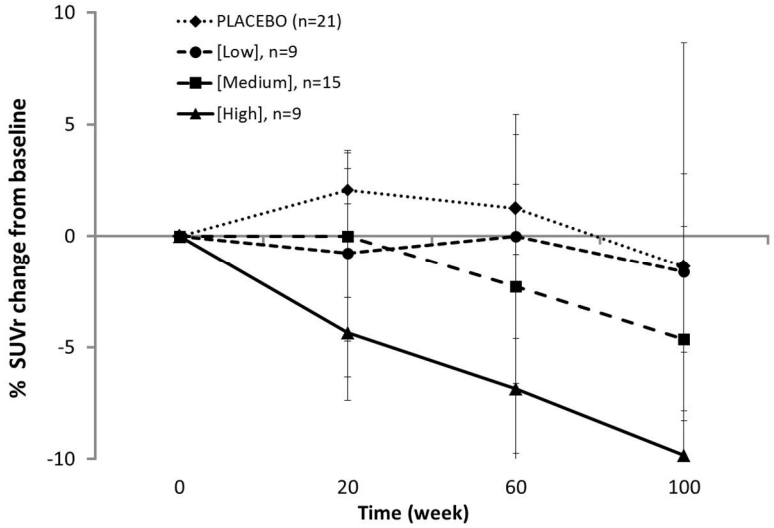
Figure 2 Mean Percent Change from Baseline in Composite Amyloid PET SUVr by Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.

In Study WN25203, a concentration-based analysis of the PET results showed a clear response relationship between gantenerumab concentration in plasma and SUVr reduction, with greater mean concentrations resulting in greater amyloid clearance. As depicted in Figure 3, small changes in SUVr were present in the placebo and 1.9–5-μg/mL gantenerumab groups, whereas the 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 3 Median Changes over Time in Concentration-Dependent PET SUVr by Gantenerumab Serum Concentration and Cerebellum Gray Reference: Study WN25203, PET Substudy



PET = positron emission tomography; SUVr = standardized uptake value ratio.
Note: low = 1.9–5 μg/mL; medium = 5–10 μg/mL; high = 10–20.7 μg/mL.

In addition, CSF analyses performed in Study WN25203 showed dose-dependent reductions in both CSF tau species (total tau [t-tau] and phosphorylated tau [p-tau]) in patients receiving gantenerumab compared with placebo. No change in CSF $A\beta_{42}$ was present over the 2-year period, as expected, given the mechanism of action of gantenerumab that targets fibrillar over monomeric Aβ.

Overall, these findings indicate the presence of clinical and biological effects of gantenerumab in subjects who had the highest exposure. In overall study population, results from the futility analysis of Study WN25203 indicated that the likelihood of the 225-mg dose of gantenerumab achieving a clinical effect was very low. These findings indicate that higher doses are required to achieve a clinical effect associated with the biological activity indicated by the amyloid and tau biomarker findings in Study WN25203. As a result, the decision was made to convert Studies WN25203 and WN28745 into OLE studies to give all patients the opportunity to receive higher doses of gantenerumab and to assess the safety of higher doses.

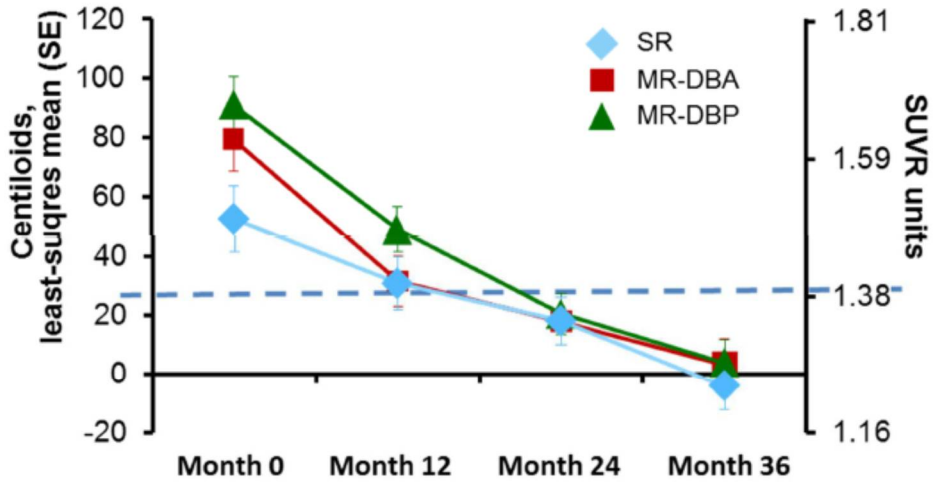
Additional support for using higher doses of gantenerumab comes from PK-PD models. Based on the established similarities between gantenerumab and aducanumab (see Section 1.3), a model characterizing the relationship between plasma drug concentration (PK) and PET response (i.e., the PD effect on amyloid load in the brain) was derived from both gantenerumab Study WN25203 data and aducanumab PRIME data to determine the target dose of gantenerumab for the OLE studies (for further details see

Appendix 4). In the OLE studies, the 1200-mg dose of SC gantenerumab Q4W is predicted to achieve plasma levels comparable to 10 mg/kg of IV aducanumab Q4W and to be associated with a comparable (~20%) amyloid brain reduction, which, in the case of aducanumab, was associated with a statistically significant clinical effect after 1 year of treatment. In order to minimize the occurrence of ARIA-E while achieving the target dose within a reasonable time frame, several titration schedules have been explored in the WN25205 OLE and WN28745 OLE studies.

Gantenerumab PK-PET models of amyloid reduction have been confirmed by PET data from the OLE studies (Klein et al. 2019). There were 89 patients from the OLE studies included in an amyloid PET substudy using [^{18}F] florbetapir (Amyvid™). Of these 89 patients, 67 received follow-up scans at Week 52 of the OLE, 42 received scans at Week 104 of the OLE, and 30 received scans at Week 156 OLE, before the cutoff date of 31 Aug 2019.

Patients were divided into three analysis cohorts because of heterogeneous baseline characteristics, time off-dose before OLE dosing, and OLE titration schedules: 1) MR-DBP (Marguerite RoAD [Study WN28745] double-blind placebo subgroup), which included patients in the placebo arm of Marguerite RoAD (Study WN28745); 2) MR-DBA (Marguerite RoAD double-blind active subgroup), which included patients in the active treatment arms of WN28745; and 3) SR (Scarlet RoAD [Study WN25203] subgroup), which included a combined cohort of all patients from the Scarlet RoAD. SR patients were combined into a single cohort because all patients were off-dose for 16–19 months prior to OLE dosing. Out of 67 patients, 27 were in the MR-DBP, 21 were in the MR-DBA, and 19 were in the SR analysis cohorts. In the OLE PET substudies, a marked and consistent reduction of amyloid load in patients receiving high-dose gantenerumab was observed (see Figure 4). Mean PET centiloid reductions from baseline were –42, –48 , and –21 at Week 52; –71 , –62 , and –36 at Week 104; and –90, –75 , and –57 at Week 156 in the MR-DBP, MR-DBA, and SR analysis cohorts, respectively (see Figure 4). Amyloid reductions are consistently seen in nearly all patients of the three analysed subgroups (see Figure 5 and Figure 6).

Figure 4 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Absolute centiloids[a]				
SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	18.2 (8.1) n = 12	**–4.1 (8.0)** n = 9
MR-DBA	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.2) n = 11	**3.3 (9.0)** n = 6
MR-DBP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.6 (6.9) n = 17	**4.0 (7.8)** n = 8

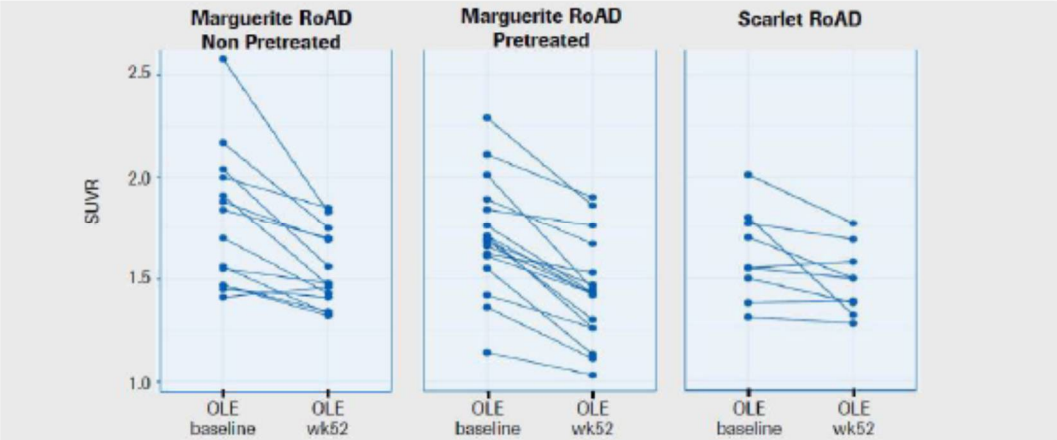
Data presented at Clinical Trials in Alzheimer's Disease (CTAD) Asia in 2019

MR-DBA = Marguerite RoAD (WN28745) pretreated subgroup; MR-DBP = Marguerite RoAD (WN28745) non-pretreated subgroup; OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (WN25203) subgroup; SUVR = standardized uptake value ratio.

[a] Analysed using a mixed-model for repeated measures.

The data from the OLE PET substudies showed higher reductions of amyloid plaque over a shorter time period with the 1200-mg dosing regimen of gantenerumab compared with the 105- or 225-mg dosing regimen. Mean amyloid levels were reduced by 39 centiloids by Week 52 and by 59 centiloids by Week 104, a 3.5-times greater reduction than was seen after 2 years at 225 mg.

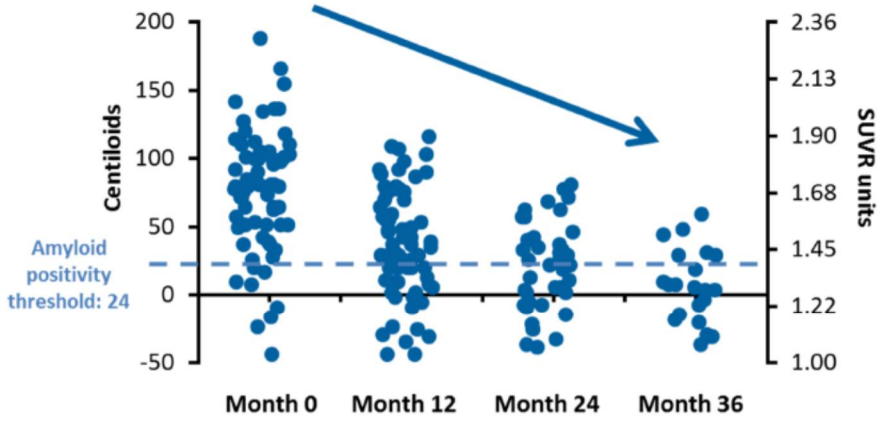
Figure 5 SUVR Reductions during the First Year of High-Dose Gantenerumab Treatment in the OLE PET Substudies



Data presented at CTAD in 2017.
OLE, open-label extension; SUVR, standardized uptake value ratio; wk, week

An important anchor for interpreting PET results is the threshold for amyloid positivity, which is the quantitative threshold that best discriminates pathologically verified absence of plaques or sparse plaques from moderate to frequent plaques. A centiloid value of 24 is generally recognized as the amyloid positivity threshold for florbetapir (Klein et al. 2019). Results in this ongoing study confirm the amyloid plaque removal component of the gantenerumab mechanism of action and show that following two years of treatment, 51% of subjects achieved below-threshold PET SUVr signals based on quantitative measures and that 74% of subjects were below threshold after three years of treatment (see Figure 6).

Figure 6 Patient-Level Amyloid Reductions Over 3 Years of Treatment in the OLE PET Substudies



Proportion of patients below amyloid positivity threshold				
No. of patients	68	67	40	23
% below threshold	15%	37%	51%	74%

Data presented at CTAD Asia in 2019
SUVR, standardized uptake value ratio

1.3.2 Rationale for Dosing Strategy

As indicated in Section 1.3.1, the target dose of 1200 mg G3 material administered in the WN25203 and WN28745 OLE studies has been identified based on PK-PD modeling and simulations (details about the model are presented in Appendix 4) and is predicted to lead to an amyloid PET reduction similar to 10 mg/kg IV aducanumab Q4W. The OLE PET data have been consistent with these predictions.

In the OLE Studies WN25203 and WN28745, patients were allocated to different titration schedules (two schedules in Study WN25203 and four schedules in Study WN28745) according to their *APOE* allele status and treatment arm during the double-blind period of the parent studies. These titration schedules were implemented in order to mitigate the risk of ARIA events. An ARIA-E hazard model was first developed on bapineuzemab data (Hutmacher et al. 2013). This model, which includes drug concentrations, time since first dose, and *APOE* ε4 allele status, was applied to the double-blind results in Study WN25203; the model was then tested on publicly available aducanumab data from the PRIME study and were used to predict the incidence of ARIA-E events with a high degree of accuracy, including the observed ARIA-E rate differences across *APOE* ε4 allele groups.

Recently, the ARIA-E hazard model has been updated with observations from the WN25203 and WN28745 OLE trials using higher doses of gantenerumab (see Appendix 5).

Using the validated PK-PET and ARIA-E hazard model, multiple titration options have been simulated, including separate simulations for *APOE* ε4 allele carriers and non-carriers. Two different types of titration schedules, reflecting the different risk for ARIA events between *APOE* ε4 allele carriers and non-carriers were considered. Although an *APOE* ε4 genotype–based titration regimen could permit *APOE* ε4 non-carriers to achieve the target dose more quickly, an option with a single, slower titration schedule for all patients is favored as it provides an overall lower risk for ARIA. Given the chronic and gradually progressive nature of AD, the favored option is a single, slow titration schedule for all patients because it is simpler for clinicians, less prone to error, and does not require *APOE* genotyping before the initiation of treatment.

Thus, based on the information from the WN25203 and WN28745 OLE studies, in which gantenerumab (manufactured with G3 process) up to 1200 mg Q4W was assessed and shown to be safe for APOE ε4 allele carriers and non-carriers, and based on the internally developed PK-PD models, the following dosing regimen for Study WN29922 was selected: 150 mg Q4W for 3 months, then 300 mg Q4W for 3 months, and then 600 mg Q4W for 3 months, followed by 600 mg Q2W until the end of the study. The switch to a Q2W administration schedule allows patients to decrease the number of SC administrations in the abdomen per visit.

The PK-PD models referenced above were developed based on information from the G3 material and were used to establish the initial dosing regimen for this study. As indicated previously, gantenerumab drug substance manufacturing process was optimized from G3 to G4, and a relative bioavailability study (WP40052) assessed the pharmacokinetic difference between the G3 and G4 material in humans.

The results of this relative bioavailability study (WP40052) show that the AUC_{inf} is approximately 1.18 fold and the C_{max} is approximately 1.05 fold higher after administration of G4 compared with G3. As AUC is considered the driver of the treatment effect, the conversion factor of 1.18 from the G3 to G4 material has been based on the AUC_{inf}. The association between microglial-driven removal of aggregated brain amyloid and AUC has been shown in preclinical experiments and clinical studies. In addition, as gantenerumab exhibits linear pharmacokinetics, the AUC_{inf} after single dose reflects the steady state exposure (AUC_{tau}) after multiple doses.

Based on the above rationale and the fact that gantenerumab manufactured with G4 process was safe and well tolerated, the G3 dosing regimen has been converted into the following G4 dosing regimen for the WN29922 study: 120 mg Q4W for 3 months, then 255 mg Q4W for 3 months, and then 510 mg Q4W for 3 months, followed by 510 mg Q2W until the end of the study. This schedule enables titration to target dose within 9 months (see Table 1), with predicted overall ARIA-E rate of approximately 26% based on the current ARIA-E hazard model. The low starting doses and gradual increase in dosing (i.e., slow titration schedule) are expected to reduce the risk of ARIA-E for both

APOE carriers and non-carriers. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

Table 1 Proposed Dose and Titration Regimen for Phase III Studies

Month	1	2	3	4	5	6	7	8	9	10
Dosing frequency	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q4W	Q2W
Dose (mg)	120	120	120	255	255	255	510	510	510	510

1.3.3 Risk-Mitigation Measures for ARIA Findings

ARIA is the most significant adverse event reported in therapies against aggregated forms of Aβ. These findings appear to be dose, time, and *APOE* ε4 allele dependent (Piazza and Winblad 2016).

The mechanism underlying the development of ARIA-E and ARIA-H during anti-amyloid treatment is unknown. Because antibodies target removal of Aβ from both the parenchyma and 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 consists of proteinaceous fluid and in ARIA-H if the leakage consists of blood products (Sperling et al. 2012).

Thus, an anti-Aβ therapy that effectively maintains vascular β-amyloid clearance would allow vascular remodeling and may, with time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experience in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Previous and ongoing studies with gantenerumab showed that ARIAs are manageable with MRI monitoring and dose intervention algorithms (i.e., temporary study drug interruption or temporary suspension of uptitration) and that these events are mostly asymptomatic. Data from the long-term extension of the PRIME study (aducanumab) suggested also that a titration up to 10 mg/kg (predicted to be comparable to 1200 mg of SC Q4W G3 gantenerumab (or 510 mg of SC Q2W G4 gantenerumab) per the PK-PD model (see Appendix 4) may reduce the incidence of ARIA-E compared with higher fixed dosing (Viglietta et al. 2016).

In Study WN29922, imaging-related criteria are used to exclude patients with clinically important cerebral vascular disease at baseline, as well as ARIA-related lesions. A slow titration schedule will be implemented to reach the target dose, and MRI monitoring will be conducted during the study at regular intervals (see Appendix 1 for the schedule of activities for the uptitration and MRI schedules). An MRI scan documenting the absence of ARIA-E findings will be required prior to each dose increase. If ARIA findings occur, more intense MRI monitoring, dose adjustments, temporary dose holding, or permanent

discontinuation will be implemented according to an ARIA-related dose-adjustment plan, described in Section 5.1.2. Safety findings (including unblinded individual patient and aggregate data) will be reviewed on a regular basis by the iDMC.

1.3.4 Risk to Participants without Alzheimer's Disease Pathology

Owing to the rigorous screening procedures in this study, including measurement of the CSF tau to $A\beta_{42}$ ratio and/or amyloid PET scan, it is anticipated that only participants with AD pathology will be enrolled. In the event that a participant without amyloid pathology is enrolled, no additional risk is expected. However, such participants may still experience side effects related to administration of gantenerumab (e.g., ISRs and development of anti-drug antibodies [ADAs]).

1.3.5 Overall Benefit–Risk Summary

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

- Gantenerumab has shown evidence of reducing amyloid plaques (i.e., observed evidence of brain amyloid reduction) and, thus, shows potential benefit in slowing the progression of AD.
- Findings from the WN25203 and aducanumab PRIME studies provide additional support for the hypothesis 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, showed that ARIA findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment. ARIAs are manageable with MRI monitoring and dose intervention algorithms, as detailed in Section 5.1.2.
- No new safety signal has been identified in the data from the ongoing OLE studies with doses of up to 1200 mg Q4W G3 material. These data support the administration of the target dose of 510 mg Q2W G4 material to both ApoE ε4 carriers and non-carriers in the WN29922 study.
- *The benefit risk ratio of conducting the WN29922 study during the pandemic remains unchanged. This is supported by the preclinical and clinical data collected through the development program of gantenerumab where there has been no indication that gantenerumab administration compromised the immune system or made individuals more susceptible to infections.*
  *Thus, there are no data or biological rationale suggesting that G*antenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more severe coronavirus disease 2019 (COVID-19) outcomes.
  Participating in study visits at the investigational sites may however increase the risk of exposure to SARS-COV-2, therefore, whenever appropriate, the Sponsor allows the possibility to perform home visits by adequately trained health care professionals. All necessary precautions will be taken to protect the health of the study participants and minimize the risk of exposure. As such the PI, in addition to

all appropriate study staff that come into contact with the study participants, will wear personal protective equipment during the visit as per local requirements.

Thus, the anticipated benefit–risk profile of gantenerumab supports clinical trials with higher doses in the population with early (prodromal to mild) AD.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the efficacy and safety of gantenerumab compared with placebo in participants with early (prodromal to mild) AD. Specific objectives and corresponding endpoints for the study are outlined in Table 2 for the double-blind treatment period and in Table 3 for the OLE period.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period

Primary Efficacy Objective	Corresponding Endpoint
• To evaluate the efficacy of gantenerumab administered by SC injection compared with placebo	The change from baseline (Day 1) to Week 116 [a] in global outcome, as measured by the CDR-SOB
Secondary Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo on cognition and function	The change from baseline to Week 116 [a] in cognition and/or function as measured by: • MMSE total score • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL total score and instrumental score
Exploratory Efficacy Objectives	**Corresponding Endpoints**
• To evaluate the efficacy of gantenerumab versus placebo	The change from baseline to Week 116 [a], in the following: • Clinically evident decline *as measured using the CDR* • Severity, as assessed by the CDR Global Score • Dependence level, as derived from the ADCS-ADL score • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by a total of 24 weeks, the endpoints will be based on change from baseline to Week 128.

Table 2 Objectives and Corresponding Endpoints for the Double-Blind Treatment Period (cont.)

Safety Objective	Corresponding Endpoints
• To evaluate the safety of gantenerumab compared with placebo	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline (in active treatment group only)
Pharmacodynamic Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change from baseline *to Week 116* in brain amyloid load, as measured by amyloid PET scan in a subset of participants • Change from baseline *to Week 116* in brain tau load, as measured by tau PET scan in a subset of participants • Change from baseline *to Week 116* in cerebral spinal fluid markers of disease in a subset of participants, including total tau, and phosphorylated tau
Exploratory Biomarker Objective	**Corresponding Endpoints**
• To evaluate the effect of gantenerumab compared with placebo in participants with early (prodromal to mild) Alzheimer's disease	• Change over time in plasma *and other CSF* biomarkers (see Section 4.5.6.2) • Change from baseline to Week 116 [a] in functional brain connectivity, as measured by resting-state functional MRI (where available) • Change from baseline to Week 116 [a] in integrity of white matter, as measured by DTI-MRI (where available) • *MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, in all participants*
Exploratory Pharmacokinetic Objective	***Corresponding Endpoint***
• *To characterize the PK profile of gantenerumab*	• *Plasma concentration of gantenerumab (administered subcutaneously) at specified timepoints*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

[a] If the double-blind treatment period is extended by 24 weeks, the final endpoints will be based on change from baseline to Week 128.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period

Safety Objective	Corresponding Endpoints
• To evaluate the long-term safety and tolerability of SC gantenerumab in participants with early AD	• Nature, frequency, severity, and timing of adverse events and serious adverse events • Physical examinations (including neurological systems), vital signs, blood tests, ECGs, and C-SSRS • Nature, frequency, severity, and timing of MRI findings: ARIA-E and ARIA-H • Nature, frequency, severity, and timing of injection-site reactions • Presence of ADAs during the study relative to the presence of ADAs at baseline
Exploratory Efficacy Objective	**Corresponding Endpoints**
• To assess the long-term efficacy of SC gantenerumab in participants with early AD	• The change in cognition, function and other outcomes over time, as measured by: • CDR • MMSE • ADAS-Cog11 and ADAS-Cog13 • Verbal Fluency Task • Coding • FAQ • ADCS-ADL • Health-related quality of life, as assessed by the QoL-AD scale • Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q • Study partner burden, as assessed by the ZCI-AD scale • Elements of resource utilization, as assessed by the RUD-Lite • Health outcomes in participant and study partner, as measured by EQ-5D questionnaire

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

Table 3 Objectives and Corresponding Endpoints for the Open-Label Extension Period (cont.)

Exploratory Pharmacodynamic Biomarker Objective	Corresponding Endpoints
• To evaluate the long-term effect of SC gantenerumab in participants with early AD	• Brain amyloid load over time, as measured by amyloid PET scan in a subset of participants • Brain tau load over time, as measured by tau PET scan in a subset of participants • Cerebral spinal fluid markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau, and phosphorylated tau • MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures, functional brain connectivity, integrity of white matter in all participants • Plasma markers over time *in all participants*

Aβ = amyloid-β; AD = Alzheimer's disease; ADA = anti-drug antibody; ADAS-Cog11 = Alzheimer Disease Assessment Scale–Cognition, Subscale 11; ADAS-Cog13 = Alzheimer Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormalities–edema/effusion; ARIA-H = amyloid-related imaging abnormalities–hemosiderin deposition; CDR = Clinical Dementia Rating; CDR-GS = Clinical Dementia Rating global score; CDR-SOB = Clinical Dementia Rating–Sum of Boxes; CSF = cerebral spinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; PET = positron emission tomography; PK = pharmacokinetic; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study designed to evaluate the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD.

The planned number of participants for the global enrollment phase for the study is approximately 1016 participants randomized in a 1:1 ratio to receive gantenerumab and placebo (508 participants randomized to gantenerumab and 508 randomized to placebo) (see Section 6.1). To maintain a balanced number of participants enrolled in each treatment arm and to ensure that the arms are comparable, randomization will be stratified by stage of disease (prodromal AD vs. mild AD), APOE allele status (presence vs. absence of the ε4 allele), use of AD medication (presence vs. absent), geographic region (Western Europe and Australia vs. Rest of the World vs. North America) and participation in longitudinal amyloid and tau PET substudies. Approximately 175 centers in approximately 15 countries worldwide will participate in this study.

Participants will be selected on the basis of clinical diagnosis of probable AD (according to the National Institute on Aging/Alzheimer's Association [NIA/AA] diagnostic criteria and guidelines for AD; see Appendix 2) (McKhann et al. 2011) or prodromal AD (according to the NIA/AA diagnostic criteria and guidelines for MCI due to AD; see Appendix 3) (Albert et al. 2011). The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Eligible participants will be 50–90 years old, inclusive, must show evidence of β-amyloid pathology as indicated by the CSF tau to Aβ42 ratio (CSF-enrolled participants) or positive amyloid PET scan by visual read (PET-enrolled participants), and meet eligibility criteria as detailed in Section 4.1.

The study will consist of a screening period of up to 12 weeks in length following the signing of informed consent. Sites also have the option to prescreen participants on the FCSRT and MMSE. Participants must sign a separate Informed Consent Form before administration of these tests if used for prescreening. If the results confirm a participant's eligibility, then the FCSRT and MMSE will not have to be completed again during the screening period as long as the test has been done within 12 weeks prior the baseline.

Eligible participants will then undergo baseline visit assessments (Day 1) prior to receiving the first dose of blinded study drug (gantenerumab or placebo). Participants will continue in the double-blind treatment period.

Due to the global impact of the COVID-19 pandemic and the resulting disruption in study drug administration, the duration of the double-blind treatment period will be extended by 12 weeks, with the possibility of an additional 12-week extension (for a total of 24 weeks). This may result in the following scenarios:

- Scenario 1: Participants who are enrolled and active in the double-blind treatment period after implementation of Protocol Version 4 will have the double-blind treatment period extended by 12 weeks, with the final efficacy and safety visit at Week 116 (Appendix 1).
- Scenario 2: If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, then the Sponsor has the option to extend the double-blind treatment period by an additional 12 weeks, with the final efficacy and safety visit at Week 128 (Appendix 1). This extension will be mandatory for all patients who are active in the double-blind treatment period at the time that the extension decision is implemented.

Participants who have already had the last study drug administration at Week 102 and their final efficacy and safety visit at Week 104 and who have completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks*, will continue into the OLE of either the WN29922 study or the WN42171 study. Alternatively, they will continue into the safety follow-up period.

For participants who enroll or who are active in the double-blind treatment period at the time of implementation of *the study extension by 12 weeks*, visits and study drug administration will occur Q4W until participants reach the target dose, which will be 510 mg Q2W. After the last dose of study drug (Week 114 for scenario 1 and Week 126 for scenario 2, if applicable), final efficacy and safety assessments will be performed 2 weeks later (at Week 116 for scenario 1 and at Week 128 for scenario 2, if applicable). Participants may then enroll in an OLE study if they are eligible (either in the OLE part of this study or in the WN42171 study) or have safety follow-up visits 14 and 50 weeks after the last dose for safety and limited efficacy assessments.

All participants who prematurely discontinue treatment will continue participating in the study and will be asked to return for collection of safety and limited efficacy data (see Section 4.7.1).

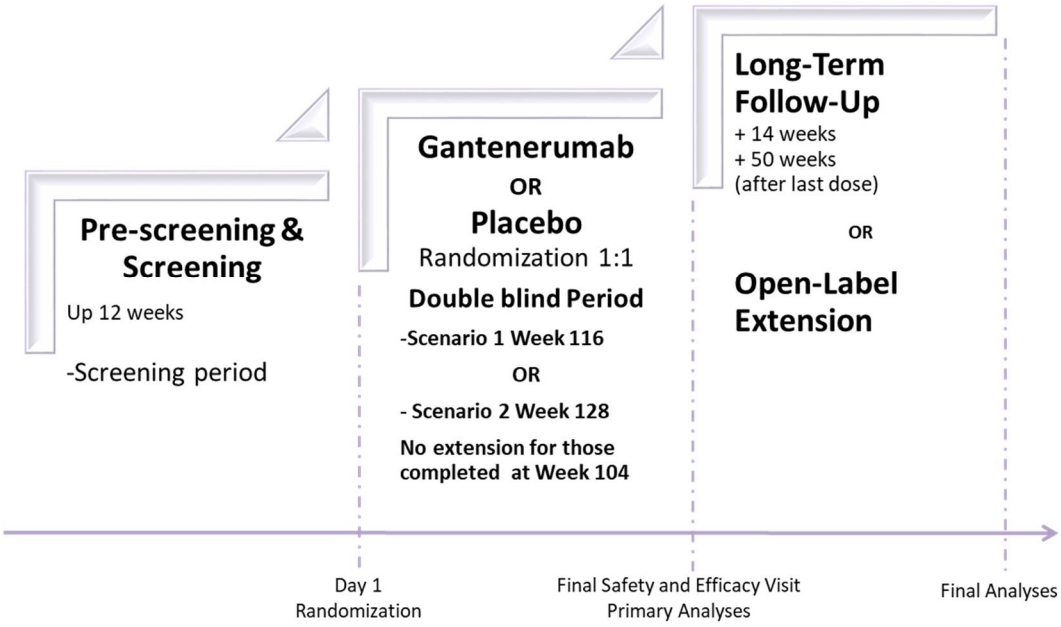
Participants will undergo brain MRI examinations for safety monitoring and longitudinal changes in brain structure. MRI scans will be read by a central MRI reader (for more details regarding imaging-related criteria, see Section 4.1.2.2). Participants will also undergo standard tests to monitor safety (blood tests, ECG), as well as the Columbia–Suicide Severity Rating Scale (C-SSRS) to monitor for suicidality, tests for cognition, function, and QoL status. Blood samples for the assessment of PK samples, PD biomarkers, and ADA will be obtained from all participants.

The incidence and nature of adverse events, serious adverse events, ARIA-E, ARIA-H, ISRs, adverse events of special interest, ECGs, and laboratory abnormalities will be assessed on a regular basis by an unblinded iDMC.

An overview of the study design is provided in Figure 7. The schedule of activities is provided in Appendix 1.

Once the double-blind treatment period is completed, participants who consent and are eligible may opt to participate in an OLE. If the stand-alone open-label study (Study WN42171) is not open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will follow the OLE procedures described in this study (Section 4.3.2.2 and Appendix 1). These participants will then transition to Study WN42171 after they have completed the entire schedule of activities in the OLE of this study and the protocol for Study WN42171 is available and approved as per local requirements. If Study WN42171 is open for enrollment at the time that a participant completes the double-blind treatment period of this study, then the participant will enroll directly in Study WN42171 and not in the OLE portion of this protocol. *The OLE of Study WN29922 is not applicable in countries that cannot run Study WN42171.*

Figure 7 Overall Study Design



W=week

The study consists of three distinct periods:

- Screening (including an optional pre-screening): The screening period may last up to 12 weeks for each eligible participant.
- Double-blind treatment period: After screening, participants who meet all eligibility criteria will be randomly assigned to one of two arms (gantenerumab or placebo) in a 1:1 ratio. Following baseline assessments, each participant will receive a minimum of nine SC Q4W administrations of study drug (uptitration period), followed by up to 40 administrations of study drug in the double-blind treatment period in scenario 1 or up to 46 administrations in scenario 2, if applicable. The last dose of study drug will be administered at Week 114 in scenario 1 and at Week 126 in scenario 2, if applicable. At the end of the double-blind treatment period, 2 weeks after the last dose, all participants will undergo the final safety and efficacy study visit. Participants who have already completed the double-blind treatment period prior to implementation of *the study extension by 12 weeks* will have received 34 SC Q2W administrations of study drug during the double-blind treatment period. The last dose will be administered at Week 102, and their final efficacy and safety visit will be at Week 104.
- Post–double-blind treatment period: After the final efficacy and safety study visit, all participants will be asked to come back for the long-term follow-up visits or to continue in the OLE.

  Long-term follow-up: Long-term follow-up will consist of a 50-week follow-up period with evaluations at Weeks 14 and 50 after completion of study drug

administration. Participants who withdraw early during the double-blind treatment period or during the OLE period are also asked to complete the long-term follow-up visits.

OLE: All eligible participants will have the opportunity to enter an OLE study.

- Eligible participants who enrolled early in the WN29922 study may start the OLE as detailed in Appendix 1, Table 5, and Table 6, and will then transition to the open-label Study WN42171 (details will be provided in Protocol WN42171). Participants who terminated the WN29922 OLE early will be asked to come back for long-term follow-up visits.
- If the WN42171 protocol is available and approved by local authorities, the eligible participants will directly be enrolled in the open-label Study WN42171.

For the schedule of activities at each visit, see Appendix 1.

China Enrollment Plan

Based on historical data, participant recruitment is expected to take longer in China; therefore, a specific China enrollment plan has been established. Thus, if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

3.1.2 Substudies

The substudies associated with Study WN29922 will be described in separate protocols, and participants consenting to enroll in these substudies will be asked to sign the associated Informed Consent Forms.

To date, there are two substudies associated with Study WN29922: a longitudinal Amyloid PET substudy and a longitudinal Tau PET substudy. The amyloid- and tau PET assessments will allow a longitudinal evaluation of the effect of gantenerumab on brain amyloid deposition as measured by florbetaben or flutemetamol PET radioligands and tau burden as measured by [^{18}F] GTP1 (an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with early AD. Details of any interim analyses relating to the substudies will *also* be described in the substudy protocols.

The PET data that are collected are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between change in florbetaben/flutemetamol/[^{18}F] GTP1-PET and changes in other endpoints in the Study WN29922.

3.1.3 Data Monitoring Committee

The iDMC will evaluate participant safety and efficacy on a regular basis. In addition to the data defined in the iDMC Charter (e.g., the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs), the iDMC will review all necessary cumulative data at regular intervals during the study, including efficacy when needed. It is anticipated that these assessments will occur approximately every 3 months. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, enrollment in a specific arm should be discontinued, the treatment regimen should be modified, the protocol should be amended, enrollment should be held pending further safety evaluations). The iDMC will also evaluate planned or unplanned interim analyses for efficacy or futility (see Section 6.7.1).

Decisions will be made in consideration of the totality of the available data. Ad-hoc meetings may be called in addition to scheduled meetings, as necessary, to provide recommendations on management of any new safety issues. Specific operational details such as the committee's composition, frequency and timing of meetings, and members' roles and responsibilities are detailed in the iDMC Charter.

Final decisions will rest with the Sponsor.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of the study is defined as the date when the last patient, last visit (LPLV) occurs or the date at which the last data point required for safety analyses or safety follow-up is received for the last participant, whichever occurs later.

The study will consist of a screening period of up to 12 weeks (including the optional prescreening period) for each eligible participant who signs the Informed Consent Form and agrees to participate, followed by a double-blind treatment period of study drug treatment plus a visit 2 weeks after the last dose. The duration of the double-blind treatment period is extended by 12 weeks (116 weeks in total in scenario 1). In case scenario 2 is implemented, the double-blind treatment period will be extended by 24 weeks (128 weeks in total in scenario 2, if applicable). For participants not entering the OLE period, this will be followed by the post–double-blind treatment period of two follow-up visits at 14 and 50 weeks after the last dose. Thus, for a participant not entering the OLE period, the maximum length of study is approximately 176 weeks in scenario 1 or 188 weeks in scenario 2 (if applicable).

For participants entering the OLE period, the extension will consist of an open-label period of at least 35 weeks. If a participant is ready to be uptitrated to the target dose and if the safety MRI allows, the participant will then be transitioned to the WN42171 open-label study. If there is an ongoing ARIA-E, the participant will remain in Study WN29922 until the ARIA-E resolves and the participant is ready to be uptitrated to the target dose. In case the dosing is temporarily interrupted for any other reason, the

participant will be kept in the WN29922 study until they are ready to be uptitrated to the target dose. Participants who are not willing to transition to the WN42171 open-label study after OLE Week 35 will be asked to come back for two follow-up visits at 14 and 50 weeks after the last dose (OLE Follow Up 1 and Follow Up 2, respectively).

3.3 RATIONALE FOR STUDY DESIGN

This is a Phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of the efficacy and safety of gantenerumab in participants with early (prodromal to mild) AD, increased amyloid burden (defined according to CSF or PET criteria), and clinical symptoms.

3.3.1 Rationale for Participant Population

As the accumulation of Aβ brain amyloid begins 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 the disease. For this reason, Roche has focused clinical development of gantenerumab on early (prodromal to mild) AD.

Participants in this study are required to meet standard research criteria for mild AD (according to the NIA/AA research criteria and guidelines for AD; see Appendix 2) or prodromal AD (according to the NIA/AA research criteria and guidelines for MCI due to AD; see Appendix 3). Note that the terms “prodromal AD” and “MCI due to AD” are considered to refer to the same population in this study and are defined according to NIA/AA research criteria and guidelines for MCI due to AD. Thus, participants with prodromal AD will present with documented objective evidence of deficit in one cognitive domain. Participants with mild AD must present with documented deficits in at least two cognitive domains and evidence of functional decline. Overall, the population will have an MMSE between 22 and 30 (inclusive) points and a CDR global score (CDR-GS) of 0.5 or 1.0. The MMSE score provides evidence of no more than mild disease severity and the CDR-GS score indicates that the participants have prodromal AD or cognitive and functional deficits consistent with mild AD. The aim of the study is to recruit approximately 50% of the participants with prodromal AD.

Gantenerumab is an antibody that targets Aβ. Thus, the study population should have documented evidence of amyloid pathology. This participant selection approach is consistent with the NIA/AA research diagnostic criteria and guidelines for AD as well as with the Qualification Opinion from the European Medicines Agency’s (EMA’s) Committee for Medicinal Products for Human Use on the use of CSF biomarkers for enrichment of trials in mild to moderate AD dementia (2012), and the U.S. Food and Drug Administration (FDA’s) draft guidance for early AD (2013). Although the FDA’s guidance refers to the early stage of AD in which individuals present with clinical MCI, biomarkers of amyloid pathology are expected to add value to participant selection in mild AD studies, especially for anti-amyloid treatments (McKhann et al. 2011; Dubois et al. 2014, 2016). Biomarker enrichment is important for anti-amyloid therapy

clinical trials because some results of early trials have demonstrated that approximately 20% participants who are enrolled in trials based on a clinical diagnosis of AD alone may not have underlying amyloid pathology as assessed by amyloid PET (Doody et al. 2014; Salloway et al. 2014).

For enrollment in this study, biomarker evidence of β-amyloid deposition will be assessed either by a centralized visual assessment of PET amyloid imaging, using one of the three following amyloid PET imaging tracers (Vizamyl™, Neuraceq™, and Amyvid™ according to country and site availability) or by the CSF tau to $A\beta_{42}$ ratio (using a prespecified cutoff and the Roche Diagnostics Elecsys immunoassay).

Both methods (CSF and PET) are established approaches to identify Aβ accumulation in the brain in vivo (Pannee et al. 2016; Vos et al. 2016) and both have been used in research and in clinical practice. There is also emerging evidence that indicates consistency between PET amyloid imaging and CSF biomarkers. Indeed, in biomarker research studies, concordance between amyloid PET and the combination of CSF $A\beta_{1-42}$ with t-tau has been shown to be very high with properly controlled CSF methodologies (EMA 2012).

To enrich for participants who are more likely to decline over the 2-year trial, all participants have to demonstrate amnestic deficits as measured by the FCSRT's total free recall score and cueing index (Sarazin et al. 2007). The use of the FCSRT to support a hippocampal-related memory deficit (Buschke 1984; Grober and Buschke 1987) has been recommended by the International Working Group (IWG-1; Dubois et al. 2007, 2010). Indeed, the core clinical symptom of AD is significant and progressive episodic memory impairment. Memory impairments because of AD are known to be hippocampal dependent and are thought to be characterized by a deficit in recall, which is often not recovered with cueing.

The FCSRT is a cued recall test that uses controlled encoding to ensure that impaired recall and cueing results are due to memory impairment and are not a failure at encoding (e.g., by means of attentional impairment). The FCSRT has demonstrated high sensitivity and specificity in differentiating participants with AD from both healthy controls and participants with other forms of dementia (Grober et al. 2008, 2010). More recently, the choice of the FCSRT as a valid clinical marker for typical prodromal AD (amnestic MCI) has been endorsed by the IWG-2 (Dubois et al. 2014) and is supported by studies showing that this test is a good tool to use for predicting progression to AD for participants with prodromal AD (Mura et al. 2014; Lemos et al. 2015). In addition, data generated from Roche datasets showed that a cueing index of ≤ 0.67 is a good predictor of cognitive decline. Therefore, the FCSRT cueing index of ≤ 0.67 and a free recall score of ≤ 27 have been selected as inclusion criteria for this study. The cueing index measures the ability of a participant to benefit from being reminded using specific cue words to recall the target word. To prevent participants who have a high free recall and who do not appear to benefit from being reminded from being included simply because

of apparent low cueing index, a free recall score of ≤27 will also be required. The FCSRT index is consistent with that published by Sarazin et al. (2007) and Auriacombe et al. (2010).

3.3.2 Rationale for Use of a Placebo Control Group

Study WN29922 is a placebo-controlled trial in which participants will be eligible for study participation whether or not participants are receiving standard-of-care medications for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements). Given that there are currently no approved disease-modifying compounds that could serve as an active control, participants will be randomized to receive gantenerumab or placebo on top of background therapies.

3.3.3 Rationale for Gantenerumab Dosage and Titration Schedule

In the OLE studies (WN28745 and WN25203), different titration schedules (based on prior double-blind treatment exposure and *APOE* ε4 status) have been utilized to enable all participants to reach a target dose of 1200 mg SC Q4W while managing the risk for ARIA with MRI monitoring and dose intervention algorithms. In addition, data from the OLE studies support treatment at a low starting dose with a gradual increase in dosing (i.e., slow titration schedule) to reach target dose and to reduce the risk of ARIA findings.

As presented in Section 1.3.2, a target dose of 510 mg Q2W along with a titration schedule with a low starting dose and gradual increase in dosing (i.e., slow titration schedule) that is expected to reduce the risk of ARIA-E for both APOE carriers and non-carriers have been identified for the current study.

Therefore, all participants in Study WN29922 (regardless of APOE ε4 status) will receive 120 mg of SC gantenerumab Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months prior to reaching target dose of 510 mg Q2W after 9 months of titration (see Section 1.3.2 for additional details about the conversion of G3 dosing regimen to G4 dosing regimen). Based on the model predictions (see Appendix 5), the overall ARIA-E rate is expected to be approximately 26%. An MRI scan, confirming the absence of ARIA-E findings, will be required prior to each dose increase.

3.3.4 Rationale for Treatment Duration

3.3.4.1 Rationale for Double-Blind Treatment Duration

According to the EMA's guidance on medicinal products for the treatment of AD and other dementias (EMA 2018) controlled clinical trials aimed at demonstrating short-term improvement in mild to moderate AD should last at least 6 months. In order to establish an effect on disease progression, a distinction between symptomatic and disease-modifying effects of a medicinal product has to be made. In addition to demonstrating a relationship between clinical outcomes and an effect on biomarkers of disease pathology, clinical improvement must be shown over a time period that is relevant to the proposed mechanism of action and the expected natural progression rate

of the disease. In AD research, long-term placebo-controlled trials are needed in order to allow time for an efficacious therapy to reverse a longstanding disease process as well as to allow time for a sufficient number of placebo-treated participants to progress. Eighteen months was assumed to be of sufficient length in some recently completed Phase III studies of anti-Aβ antibodies (EMA 2018). In prodromal disease stages, even longer studies may be necessary. In addition, placebo decline is expected to be greater in longer studies; this greater decline allows an increased potential to demonstrate a treatment effect.

A 2-year treatment duration was selected as the most appropriate duration for assessment of the primary endpoint. The duration was based on the mechanism of action of gantenerumab, which is expected to delay and reduce AD progression over time compared with control. As 9-month titration period to reach the target dose is needed, a 2-year treatment period may also be appropriate for the assessment of the primary endpoint. To capture an earlier signal of efficacy, should it be present, assessments relevant to the study objectives will also be obtained at 6, 12, and 18 months.

Measures taken globally during the COVID-19 pandemic are expected to affect the protocol-specified administration of study drug. At the date of writing Protocol Version 4, it is expected that participants will miss an average of 8 weeks of study drug administration over the course of the original 2-year study. This has the potential to decrease the power of the study (see Section 6.1 for details). To mitigate the impact of missed administrations, the double-blind treatment period is being extended by 12 weeks. The continuing impact of the COVID-19 pandemic on study procedures will be closely monitored. If the COVID-19 pandemic results in greater than anticipated disruptions to study drug administration, the Sponsor may further extend the double-blind treatment period by an additional 12 weeks (24 weeks in total).

3.3.4.2 Rationale for OLE Treatment Duration

An open-label treatment duration of at least 9 months has been selected to offer the first participants randomized in Study WN29922 open-label gantenerumab until the Protocol WN42171 open-label study is available and approved. A duration of 9 months corresponds to the uptitration period; thus, when these first participants reach the target dose, they will be able to start the WN42171 open-label study at the target dose (i.e. 510 mg Q2W).

3.3.5 Rationale for Long-Term Follow-Up

The primary objective of the long-term follow-up is to estimate the long-term safety of gantenerumab over an extended period of time. Study assessments performed 14 and 50 weeks after the last dose of study drug will be used to evaluate the effects of treatment on both efficacy and safety parameters over an extended period after study drug discontinuation. Assessments will be conducted for all participants who discontinue treatment during the double-blind treatment period, during the OLE period, or who complete the double-blind period but do not enter the OLE period or who complete the OLE period but do not enter in the WN42171 open-label study. Assessments will also allow for the exploration of the long-term effects with declining drug exposure.

3.3.5.1 Rationale for Duration of Study Follow-Up (14 Weeks)

The primary purpose of the 14-week follow-up visit (i.e., 14 weeks after the last dose) is to evaluate the long-term safety of gantenerumab. The apparent terminal half-life of gantenerumab is in the order of 24 days, and gantenerumab is cleared from plasma after approximately 16 weeks (approximately 5 half-lives). Therefore, safety assessments performed 14 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 an enduring effect of gantenerumab after treatment is stopped.

3.3.5.2 Rationale for Long-Term Follow-Up (50 Weeks)

Assessments performed 50 weeks after the last dose will be used to evaluate the long-term effects of study drug on both efficacy and safety parameters. The assessments will allow for the exploration of the long-term effects of study drug given the expected level of decline over this period. Participants will not be restricted from starting new treatment and therefore, the analysis will be considered exploratory.

3.3.6 Rationale for Primary Outcome Measure: Clinical Dementia Rating–Sum of Boxes

AD is considered a continuous disease that passes through consecutive stages without discrete transition points. Thus, the use of a single endpoint across both subpopulations of early (prodromal to mild) AD is consistent with the current understanding of AD.

Showing the benefit of new therapies for participants in the early stages of AD is challenging, owing to the lack of sensitive assessment tools. Use of the CDR-SOB as the primary outcome measure for studies of early (prodromal to mild) AD enables simultaneous demonstration of benefit on primary symptoms and clinical relevance (Aisen 2009, 2011), while also ensuring use of a clinical outcome assessment with adequate measurement properties (FDA 2013).

The Washington University CDR is a global assessment instrument that yields global scores (GS) and SOB scores. The CDR is derived from a semi-structured interview with the participant and an appropriate informant, and it rates impairment in six categories (memory, orientation, judgment and problem solving, community affairs, home and

hobbies, and personal care) on a 5-point scale for which 0 = no impairment, 0.5 = questionable impairment, and 1, 2, and 3 = mild, moderate, and severe impairment, respectively. From the six individual category ratings, or box scores, the CDR-GS is established by clinical scoring rules, for which CDR 0 = no dementia and CDR 0.5, 1, 2, or 3 = questionable, mild, moderate, or severe dementia, respectively (Morris 1993). The CDR-SOB score is a detailed quantitative general index that provides more information than the CDR-GS in participants with early (prodromal to mild) dementia (Coley et al. 2011; Cedarbaum et al. 2013). In particular, the CDR-SOB has been proposed for use in longitudinal assessment of dementia and is widely used in AD studies as a global measure of disease progression (Williams et al. 2013). The FDA's draft guidance for developing drugs for the early stages of disease suggests that a composite scale, validated in participants with early-stage disease that includes both cognition and function as a single primary efficacy outcome measure, is appropriate. The CDR-SOB is an example of a measure that fulfills these criteria (FDA 2013) and is now being utilized as the sole primary endpoint in several studies utilizing participant populations with early (prodromal to mild) AD, including the CREAD (crenezumab), PRIME (aducanumab), ENGAGE/EMERGE (aducanumab), and Clarity AD (BAN2401) studies.

3.3.7 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden and yet provide an adequate characterization of the population PK profile of gantenerumab. The PK data may be combined with available data from other gantenerumab studies and may be used to assess exposure–response relationships for relevant imaging, CSF, plasma PD biomarkers, ECGs, and efficacy and safety outcomes in participants with early (prodromal to mild) AD, as appropriate.

3.3.8 Rationale for Biomarker Assessments

The following biomarker assessments described in Sections 3.3.8.1 (CSF), 3.3.8.2 (PET imaging), and 3.3.8.3 (brain volumetry, connectivity, and fiber tract integrity) will be used to investigate the effect of gantenerumab on the underlying pathology of AD in the participant population.

3.3.8.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF $A\beta_{1-42}$ and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF $A\beta_{1-42}$ reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels may be reflective of neurodegeneration and/or tau pathology. Amyloid deposition may be the initiating event in the cascade of pathologic processes underlying AD, whereas tau pathology appears to be a subsequent event, and more associated with neurodegeneration. Therefore, t-tau and p-tau may be studied as downstream biomarkers of the primary target of anti-amyloid therapies such as gantenerumab.

Although biomarkers indicative of certain neuropathologies are not surrogate markers for efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of participants 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 participants 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. 2012) as well as in Study WN25203 with gantenerumab. In Study WN23203, CSF biomarkers were analysed for changes in multiple proteins, including $A\beta_{1-42}$, t-tau, p-tau, and neurogranin, over the 2-year period. Markers of neurodegeneration were significantly reduced in the 225-mg gantenerumab group compared with placebo over 2 years, with greater relative reduction in p-tau relative to t-tau. The greatest effect was reduction in p-tau in the 225-mg gantenerumab arm at 2 years relative to the change in the placebo arm. There was no treatment effect on CSF $A\beta_{1-42}$ (Nikolcheva et al. 2015). Because no evidence of efficacy was demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the pharmacodynamic effects of gantenerumab and the effect on 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 and additional exploratory biomarkers reflecting neurodegeneration will be assessed at baseline and following treatment. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.8.2 Positron Emission Tomography

The definitive diagnosis of AD requires the presence of progressive dementia during life and the postmortem presence of neuropathological lesions (i.e., neuritic plaques composed of β-amyloid aggregates and neurofibrillary tangles formed from hyperphosphorylated tau protein). However, imaging approaches using ligands that demonstrate high affinity for aggregated amyloid are able to provide an assessment of deposition in vivo, which can be evaluated over time (Clark et al. 2011).

3.3.8.3 Brain Volumetry, Connectivity, and Fiber Tract Integrity

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 participants 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 (Li and Wahlund 2011). Based on volumetric MRI measurements, the two most established markers of disease

progression in longitudinal observational studies are hippocampal and whole brain atrophy (Fox et al. 2000, 2005; Jack et al. 2010), with ventricular expansion a 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. 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 participants will be assessed using a blood oxygenation level-dependent (BOLD) resting-state functional MRI (rs-fMRI) procedure (at sites where this procedure is available) with a paradigm-free procedure (Grecius et al. 2004; Filippi and Agosta 2011). Increased concentrations of Aβ in the brains of participants with AD contribute to neuronal degeneration in the brain over time and have been associated with reduced 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. It has also been found to be decreased in cognitively normal elderly participants 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 participants with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found already 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 participants with AD, may help to reverse the altered functional connectivity presumably caused by the accumulation of Aβ in the brain.

The integrity of white matter tracts will be assessed prior to and after treatment with gantenerumab using diffuse tensor imaging (DTI)-MRI techniques. DTI-MRI is based on the measurement of diffusion properties of water molecules in the axonal fiber tracts in white matter. Whereas water molecules can diffuse isotropically in CSF, they are restricted axially in white matter bundles. Widespread group differences in the degree of anisotropic diffusion, or fractional anisotropy (FA), has been seen between participants with AD and healthy subjects (Jack et al. 2015). Greater FA values are thought to indicate greater white matter integrity. Likewise, mean diffusivity, which measures the average rate of diffusion in all directions, has been shown to be higher in AD groups compared with healthy controls, presumably owing to increased white matter injury in participants with AD (Nir et al. 2013).

At sites having the required software and hardware, rs-fMRI (BOLD rs-fMRI) and DTI-MRI will be performed when feasible during the same scanning session as the structural MRI to assess functional brain connectivity and fiber tract integrity before and after treatment with gantenerumab.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS WITH ALZHEIMER'S DISEASE

This study will enroll approximately 1016 participants with increased brain amyloid burden (defined according to CSF or PET criteria), objective memory impairment indicated by cognitive assessment, and a diagnosis of probable AD or prodromal AD based on relevant NIA/AA criteria during the global enrollment phase. Additional criteria are defined in Sections 4.1.1 and 4.1.2.

An increase in sample size may be considered in the event of changes to the sample size assumptions on the basis of blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in China. All participants enrolled at NMPA-recognized sites in the global enrollment phase will be included in the primary analysis. All participants enrolled at NMPA-recognized sites in the global enrollment phase and the China extension phases will be included in a China-specific analysis. Details will be provided in the SAP.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Ability to provide written consent signed by the participant (co-signed by the participant's legally authorized representative, if required by the local regulations, guidelines, and independent Ethics Committee [EC] or Institutional Review Board [IRB])
- Age 50–90 years old at screening, inclusive
- Availability of a person (referred to as the "study partner" throughout this protocol) who:
  - Agrees to participate throughout the duration of study
  - In the investigator's judgment, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant
  - In the investigator's judgment, is able to provide accurate information regarding the participant's cognitive and functional abilities, including knowledge about domestic activities, hobbies, routines, social skills, and basic activities of daily life; work and educational history; cognitive performance including memory abilities, language abilities, temporal and spatial orientation, judgment and

problem solving; emotional and psychological state; and can report any changes in the general health status

- Agrees to provide information and to complete all aspects of the study at clinic visits (which require partner input for scale completion)
- Signs the necessary Informed Consent Form(s), and has sufficient cognitive capacity to accurately report on the participant's behavior as well as cognitive and functional abilities
- Is fluent in the language used at the site and has sufficiently good general health to have a high likelihood of maintaining the same level of interaction with the participant and participation in study procedures throughout the duration of the study

Every effort should be made to have same study partner participate throughout 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 [if applicable], clinical genotyping, and PET imaging [if applicable])

The participant should be capable of completing assessments either alone or with the help of the study partner.

- Adequate visual and auditory acuity, in the investigator's judgment, sufficient to perform the neuropsychological testing (eye glasses and hearing aids are permitted)
- Evidence of AD pathological process, as confirmed by CSF tau/$A\beta_{42}$ or on amyloid PET scan by qualitative read by the core/central PET laboratory
- Demonstrated abnormal memory function at screening (FCSRT cueing index ≤ 0.67 and free recall ≤ 27)
- Screening MMSE score ≥ 22 and CDR-GS of 0.5 or 1.0
- Probable AD dementia (consistent with NIA/AA core clinical criteria for probable AD dementia) (McKhann et al. 2011) or prodromal AD (consistent with the NIA/AA diagnostic criteria and guidelines for mild cognitive decline due to AD) (Albert et al. 2011)
- If the participant is receiving symptomatic AD medications, a stable dosing regimen for at least 3 months prior to screening and until randomization

Participants receiving GV-971 or who are planning to take GV-971 during the study are not eligible

- 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
- For enrollment in the China extension, participants must have residence in mainland China, Hong Kong, or Taiwan and be of Chinese ancestry

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraceptive methods that result in a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the last dose of study drug

  A woman is considered to be of childbearing potential if she is postmenarcheal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

  Examples of contraceptive methods with a failure rate of $<1\%$ per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.

  The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the participant. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception.

4.1.2 Exclusion Criteria

4.1.2.1 Exclusions Related to Central Nervous System Disorders

Participants who meet any of the following criteria related to CNS disorders will be excluded from study entry:

- Any evidence of a condition other than AD that may affect cognition, including, but not limited to, frontotemporal dementia, dementia with Lewy bodies, vascular dementia, Parkinson disease, corticobasal syndrome, Creutzfeldt-Jakob disease, progressive supranuclear palsy, frontotemporal lobar degeneration, Huntington disease, normal pressure hydrocephalus, seizure disorder, delirium or hypoxia
- History or presence of clinically evident systemic vascular disease (e.g., clinically significant carotid/vertebral artery stenosis or plaque, aortic aneurysm), that in the opinion of the investigator has the potential to affect cognitive function
- History or presence of clinically evident cerebrovascular disease (e.g., intracranial or cerebral vascular malformations, aneurysm, intracranial macrohemorrhage)

  Participants with asymptomatic developmental venous anomalies may be eligible after discussion with and approval by the Medical Monitor.
- History or presence of posterior reversible encephalopathy syndrome
- History or presence of any stroke with clinical symptoms within the past 12 months, or documented history within the last 6 months of an acute event that is consistent, in the opinion of the investigator, with a transient ischemic attack
- History of severe, clinically significant (persistent neurologic deficit or structural brain damage) CNS trauma (e.g., cerebral contusion)
- History or presence of intracranial mass (e.g., glioma, meningioma) that could potentially impair cognition

- Presence of infections that affect brain function or history of infections that resulted in neurologic sequelae (e.g., HIV, syphilis, neuroborreliosis, and viral or bacterial meningitis and encephalitis)
- History or presence of systemic autoimmune disorders that potentially cause progressive neurologic disease with associated cognitive deficits (e.g., multiple sclerosis, lupus erythematosus, anti−phospholipid antibody syndrome, and Behçet disease)
- History of schizophrenia, schizoaffective disorder, major depression, or bipolar disorder

  History of major depression is acceptable if participant has had no episode within the past year or is considered in remission or depression is controlled by treatment.
- At risk for suicide in the opinion of the investigator
- Alcohol and/or substance abuse or dependence (according to the criteria specified in the Diagnostic and Statistical Manual of Mental Disorders, Version 5) within the past 2 years

  Nicotine use is allowed.

  Marijuana use is not allowed and must be discontinued at least 3 months before screening.

4.1.2.2 Imaging-Related Criteria

Participants who meet any of the following imaging criteria will be excluded from study entry:

- According to the MRI central reader, MRI evidence of any of the following:
  - >2 lacunar infarcts
  - Any territorial infarct >1 cm^3
  - Any white matter lesion that corresponds to an overall Fazekas score of 3 that requires at least one confluent hyperintense lesion on the FLAIR sequence, which is ≥ 20 mm in any dimension
- Combined number of microbleeds and areas of leptomeningeal hemosiderosis (i.e., cumulative ARIA-H) on MRI more than five (and should not include any disseminated leptomeningeal hemosiderosis) 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 not compatible with MRI, 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

Participants who meet any of the following criteria related to cardiovascular disorders will be excluded from study entry:

- History or presence of clinically symptomatic atrial fibrillation requiring maintenance therapy

  Participants who experienced non-valvular atrial fibrillation that resolved more than 1 year ago and was not associated with prior stroke are eligible.
- Within the last year, unstable or clinically significant cardiovascular disease (e.g., myocardial infarction)

  Heart failure classified as New York Heart Association Class I or II cardiac disease is allowed if not associated with hospitalization within the previous 12 months.
- Uncontrolled hypertension (e.g., blood pressure generally >160 mmHg systolic or >95 mmHg diastolic)

4.1.2.4 Hepatic and Renal Disorders

Participants who meet any of the following criteria related to hepatic and renal disorders will be excluded from study entry:

- Chronic kidney disease, indicated by creatinine clearance <30 mL/min to be calculated by the central laboratory using the Cockcroft-Gault formula at screening, which remains <30 mL/min if retested
- Confirmed and unexplained impaired hepatic function as indicated by screening AST or ALT $\geq 3\times$ the ULN or total bilirubin $\geq 2\times$ ULN

4.1.2.5 Infections and Immune Disorders

Participants who meet any of the following criteria related to infections and immune disorders will be excluded from study entry:

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

4.1.2.6 Metabolic and Endocrine Disorders

Participants who meet any of the following criteria related to metabolic and endocrine disorders will be excluded from study entry:

- Abnormal thyroid function as indicated by abnormal screening tests that are judged to be clinically significant by the investigator, or abnormal thyroid function that requires a new treatment or an adjustment of current treatment

  A participant may be rescreened if there is no improvement in cognition in the investigator's judgment after 3 months of adequate treatment for thyroid function.

- Participants with evidence of folic acid deficiency (as indicated by folic acid level below the lower limit of normal) or vitamin B-12 deficiency (as indicated by vitamin B-12 level below the lower limit of normal and/or methylmalonic acid levels above ULN)

  A participant may be rescreened if there is no improvement in cognition after 3 months of adequate treatment for folic acid or vitamin B-12 deficiency.

- Screening hemoglobin A_{1c} (HbA_{1C}) $>8\%$ (retesting is permitted if slightly elevated) or poorly controlled insulin-dependent diabetes (including hypoglycemic episodes)

  A participant may be rescreened after 3 months to allow optimization of diabetic control.

4.1.2.7 Exclusions Related to Medications

The following medications are prohibited for a pre-specified duration prior to study start, as indicated, and during the entire period of study participation (participants who start these medications during the study may be withdrawn from study treatment):

- Any previous administration of gantenerumab or active immunotherapy (vaccine) that is being evaluated to prevent or postpone cognitive decline
- Any passive immunotherapy (immunoglobulin) or other long–acting biologic agent to prevent or postpone cognitive decline within 1 year of screening
- Any other investigational treatment within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Any previous treatment with medications specifically intended to treat Parkinson symptoms or any other neurodegenerative disorder within 1 year of screening and with no plans to initiate such medications prior to randomization

  Certain medications are acceptable if the participant is taking the medicine for a non-neurodegenerative disorder, such as restless leg disorder (e.g., pramipexole).

- Typical antipsychotic or neuroleptic medication within 6 months of screening and with no planned changes prior to randomization except as brief treatment for a non-psychiatric indication (e.g., emesis)

Atypical antipsychotic medications are not allowed except for intermittent short-term use and will need to be discontinued 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Anticoagulation medications within 3 months of screening with no plans to initiate any prior to randomization

  Anti-platelet treatments (e.g., aspirin, clopidogrel, and dipyridamol) are permitted.

  Short-term, perioperative use of anticoagulant medications will not result in permanent discontinuation from the study; however, *for any* such use *it is recommended to* prospectively *seek advice from* the Medical Monitor and temporary study drug interruption *may be required*.

- Chronic use of opiates or opioids (including long-acting opioid medication) within 3 months of screening with no plans to initiate any prior to randomization

  Intermittent short-term use of short–acting opioid medications for pain is permitted except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) within 1 month of screening and throughout the study
- Chronic use of benzodiazepines, barbiturates, or hypnotics from 3 months before screening and with no plans to initiate any prior to randomization

  Intermittent short-term use of benzodiazepines, buspirone, or short-acting hypnotic medication for sleep or anxiety is allowed except within 2 days or 5 half-lives (whichever is longer) prior to any neurocognitive assessment.

4.1.2.8 Other Exclusions

Participants who meet any of the following criteria will be excluded from study entry:

- Other causes of intellectual disability that may account for cognitive deficits observed at screening (e.g., static encephalopathy, closed brain injury, mental retardation)

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

- Pregnancy or breastfeeding, or intention of becoming pregnant during the study
- Deformity of the lumbosacral region of the spine that in the opinion of the investigator would contraindicate lumbar puncture in participants who will have lumbar puncture
- Clinically significant abnormal screening blood, CSF (if applicable), or urine results that remain abnormal at retest
- Impaired coagulation (screening prothrombin time [PT] $> 1.2\times$ the ULN that remains abnormal on retest)
- History of cancer, with the following exceptions:
  - If considered to be cured

  - If not being actively treated with anti-cancer therapy or radiotherapy and, in the opinion of the investigator, is not likely to require treatment in the ensuing 5 years
  - For prostate cancer 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 excipients
- Any other severe or unstable medical condition 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 participant at special risk, bias the assessment of the clinical or mental status of the participant to a significant degree, interfere with the participant'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: Participants who subsequently require residence in such facilities during the study may continue in the study and be followed for efficacy and safety, provided that they have a study partner who meets the minimum requirement

4.1.3 Eligibility for the Open-Label Extension

Participants who have been randomized and who have completed the double-blind treatment period will be eligible to participate in the OLE, provided they do not meet any of the following criteria:

- Discontinued from study treatment during the double-blind treatment period.
- Received any other investigational medication during the double-blind treatment period or after the end of double-blind treatment.
- Participation in the OLE deemed inappropriate by the investigator (e.g., any serious medical condition or other concerns that preclude the participant's safe participation in the OLE or ability to comply with the required procedures).
- Presence of ARIA-E findings at the Week *116 (or Week 128, if applicable)* MRI scan (participants who have ongoing ARIA-E findings at the Week *116 [or Week 128, if applicable]* will stay in the double-blind treatment period until the finding is deemed resolved). *For those participants who enroll into the GRADUATE OLE from Week 104, before the double-blind extension took place, eligibility for the OLE would be based on the Week 104 scan.*

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

Randomization will be performed centrally using an interactive voice or Web-based response system (IxRS). After screening, participants who meet all eligibility criteria will be randomly assigned to one of two treatment groups (gantenerumab or placebo). The ratio will be 1:1, one active to one placebo. The randomization method will be stratified block-randomization. Randomization to treatment allocation will be stratified by

geographic region (Western Europe and Australia vs. Rest of the World vs. North America), participant *APOE* ε4 status (carrier vs. non-carrier), participant stage of disease (prodromal vs. mild AD), use of AD medication (present vs. absent), and participation in the longitudinal amyloid and tau PET substudies. Except in circumstances in which a health authority, EC, or IRB requires it, a participant will not be told of his or her *APOE* ε4 status. Individual participant *APOE* ε4 genotype results will be blinded to participants, investigators, and the Sponsor. *APOE* ε4 status information will be supplied directly to the IxRS vendor by the central testing laboratory so that the information can be incorporated at the time of randomization. For participants for whom *APOE* ε4 status is already known, the results will be blinded to the Sponsor and as much as possible to the site and central MRI reader.

The study is to be conducted in a double-blind manner to minimize potential bias from investigators and participants. The Sponsor will be blinded to study treatment. Sponsor, participants, and site staff will remain blinded to previous treatment allocation in the OLE period. The Master Randomization or Master Medication List will not be available at the study center, to Roche monitors, Roche project statisticians, or to the project team at Roche. Unblinding should not occur except in the case of emergency situations where knowledge of the study drug assigned would affect participant care. The investigator should make every effort to contact Roche before unblinding a participant. In the event that the investigator unblinds a participant without prior notification, the investigator must contact Roche within 1 working day of the event. Any request from the investigator for information about the treatment administered to study participants for another purpose must be discussed with the Medical Monitor.

If unblinding is necessary for participant management (e.g., in the case of a serious adverse event for which participant management might be affected by knowledge of treatment assignment), the investigator will be able to break the treatment code by contacting the IxRS. Treatment codes should not be broken except in emergency situations. If the investigator wants to know the identity of the study drug for any other reason, he or she should contact the Medical Monitor directly. The investigator should document and provide an explanation for any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event).

For regulatory reporting purposes, and if required by local health authorities, the Sponsor will break the treatment code for all serious, unexpected suspected adverse reactions (see Section 5.2.2) that are considered by the investigator or Sponsor to be related to study drug.

4.3 STUDY TREATMENT

The IMP for this study is gantenerumab.

4.3.1 Formulation, Packaging, and Handling

4.3.1.1 Gantenerumab and Placebo

Gantenerumab and placebo will be supplied by the Sponsor as liquid formulation ready for SC administration. 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 Investigator's Brochure.

For information on the formulation and handling of gantenerumab, see the pharmacy manual and Gantenerumab Investigator's Brochure.

4.3.2 Dosage, Administration, and Compliance

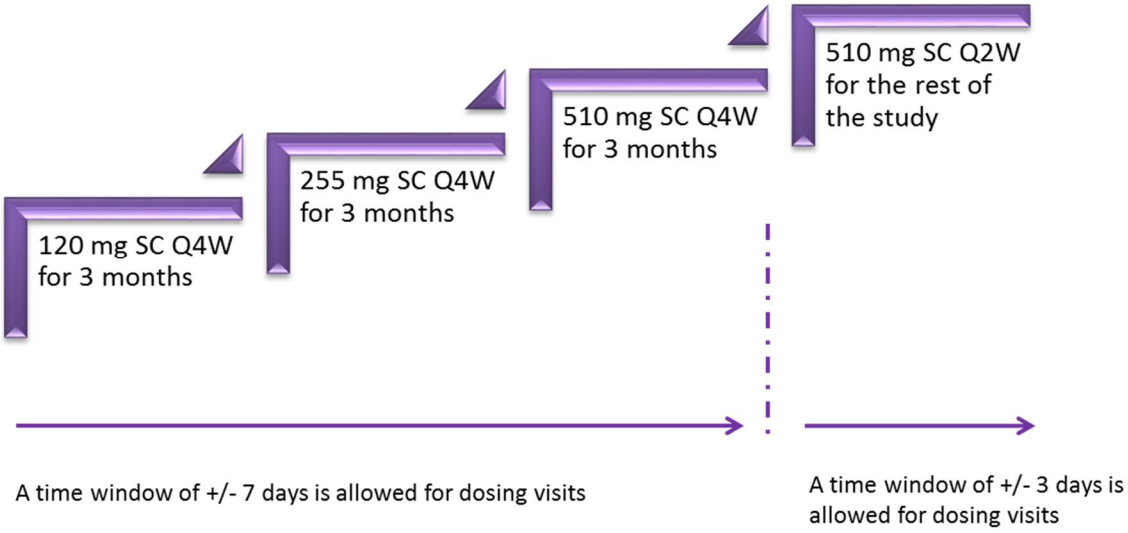
4.3.2.1 Gantenerumab and Placebo Administration during Double-Blind Treatment Period

Gantenerumab or placebo will be administered by SC injection to all participants.

Gantenerumab will be administered by SC injection to all participants randomized to the active treatment arm, regardless of *APOE* ε4 status, at a dose of 120 mg SC Q4W for 3 months, 255 mg SC Q4W for 3 months, and 510 mg SC Q4W for 3 months, prior to reaching the target dose (see Figure 8). Once the target dose is reached, study drug will be administered every 2 weeks (Q2W administration of 510 mg SC gantenerumab). The switch to a Q2W administration schedule allows decreasing the number of SC administrations in the abdomen per visit.

Note: A minimum of 3 doses during each dosing step must be administered prior to uptitration.

Figure 8 Overall Gantenerumab Dosing Design in the Double-Blind Treatment Period



Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

For Q4W injections, a time window of ±7 days is allowed for dosing visits. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Once study drug is administered Q2W, the time window for dosing visits is ±3 days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to the initial planned schedule per randomization for subsequent visits.

Regardless of dose, each participant will undergo up to a total of 49 dosing visits in scenario 1 or 55 dosing visits in scenario 2 (if applicable, see Section 3.3.1) in the double-blind treatment period of the study. Participants who have completed the double-blind treatment period at the time of the implementation of *the 12 week study extension*, will have undergone up to 43 dosing visits. Injections will be administered as one 0.8-mL (120-mg dose), one 1.7-mL (255-mg dose), or two 1.7-mL injections (510-mg dose) subcutaneously to the abdomen, respectively.

Placebo of identical composition (except protein) and identical volume to gantenerumab will be administered by SC injection to all participants randomized to placebo at the same frequency and using the same route of administration.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study

personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location, if the participant has given written informed consent to participate in home nursing visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

4.3.2.2 Gantenerumab and Placebo Administration during the Open-Label Extension Period

During the OLE, participants previously randomized to the active treatment arm will continue to be administered the study drug every two weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm will be required to undergo 9 months of uptitration.

In order to maintain the previous study treatment blinding (Sponsor, site, and participant), all participants will be dosed every two weeks in the OLE as illustrated in Table 4. As in the double-blind treatment period, a safety MRI has to be performed before each uptitration to ensure that the participant can be uptitrated safely to the next dose.

To ensure blinding to previous treatment, gantenerumab and/or placebo will be administered every 2 weeks as one 0.8-mL and two 1.7-mL injections or two 1.7-mL injections subcutaneously to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 4).

Note: As in the double-blind part, a minimum of 3 doses during each dosing step must be administered prior to uptitration. During uptitration in the OLE, a minimum of 3 doses of each dosing step also have to be administered prior to be eligible for uptitration**. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4).**

Table 4 Overall Gantenerumab Dosing Design in the Open-Label Extension

		Open-Label Extension																	
	Visit	Day 1	Wk 2	Wk 4	Wk 6	Wk 8	Wk 10	Wk 12	Wk 14	Wk 16	Wk 18	Wk 20	Wk 22	Wk 24	Wk 26	Wk 28	Wk 30	Wk 32	Wk 34
	Dose Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
Participants previously on placebo	Dose	120 mg Q4W						255 mg Q4W						510 mg Q4W					
	Injections (mL)	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 0.8A + 2× 1.7P	1× 0.8P + 2× 1.7P	1× 1.7A + 1× 1.7P	2 × 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	1× 1.7A + 1× 1.7P	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P	2× 1.7A	2× 1.7P
Participants previously on active	Dose	510 mg Q2W																	
	Injections (mL)	2× 1.7A + 1× 0.8P	2x 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A + 1× 0.8P	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A	2× 1.7A

A = Active treatment; Num = number; P = placebo; Wk = week

For the OLE, the time window for dosing visits is ± 3 days. Always return to the initial planned schedule per randomization for subsequent visits.

Rules for dosage modification and treatment interruption or discontinuation are provided in Section 5.1.2.

Participants enrolled in the WN29922 OLE study will have to complete the full titration scheme (i.e., at least 12 weeks on each dosing step) prior to being able to enroll in the WN42171 open-label study where they will receive 510 mg SC Q2W.

On study drug administration days that include efficacy assessments (see the schedule of activities in Appendix 1), study drug must be administered at the clinical site. Study personnel who prepare and administer the study drug must not be involved with any efficacy assessments or safety evaluations.

At applicable sites, study drug may be administered by a trained nursing professional at the participant's home or another suitable location if the participant has given written informed consent to participate in home nursing visits.

Any overdose or incorrect administration of study drug should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Adverse events associated with an overdose or incorrect administration of study drug should be recorded on the Adverse Event eCRF.

PET Tracers

All participants who are enrolled in PET substudies will be assessed by PET imaging using an appropriate PET ligand. For screening, the possible amyloid PET ligands will be florbetapir, florbetaben, and flutemetamol. According to E.U. guidance, the PET tracers, as used in the context of this study, are designated as non-IMP. In some regions, according to local regulations, these PET tracers 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, please refer to Section 5.7).

Details about the PET substudies are described in separate protocols.

4.3.3 Investigational Medicinal Product Accountability

All IMPs required for completion of this study (gantenerumab or placebo) will be provided by the Sponsor where required by local health authority regulations. The study site will acknowledge receipt of IMPs, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs either will be disposed of at the study site according to the study site's institutional standard operating procedure or will be returned to the Sponsor with the appropriate documentation. The site's method of IMP destruction must be agreed to 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 Continued Access to Gantenerumab

The Sponsor will offer continued access to Sponsor study drug (gantenerumab) free of charge to eligible patients in accordance with the Roche Global Policy on Continued Access to Investigational Medicinal Product, as outlined below.

A participant will be eligible to receive Sponsor study drug (gantenerumab) after completing the study if all of the following conditions are met:

- The participant has a life-threatening or severe medical condition and requires continued Sponsor study drug treatment for his or her well-being
- There are no appropriate alternative treatments available to the participant
- The participant and his or her doctor comply with and satisfy any legal or regulatory requirements that apply to them

A participant will not be eligible to receive Sponsor study drug (gantenerumab) after completing the study if any of the following conditions are met:

- The Sponsor study drug is commercially marketed in the participant's country and is reasonably accessible to the participant (e.g., is covered by the participant's insurance or wouldn't otherwise create a financial hardship for the participant)
- The Sponsor has discontinued development of the drug or data suggest that the drug is not effective for AD
- The Sponsor has reasonable safety concerns regarding the drug as treatment for AD
- Provision of the drug is not permitted under the laws and regulations of the participant's country
- Participant is eligible to enroll in an ongoing gantenerumab open-label study

The Roche Global Policy on Continued Access to Investigational Medicinal Product is available at the following Web site:

http://www.roche.com/policy_continued_access_to_investigational_medicines.pdf

All eligible participants will be offered to receive gantenerumab as part of an extension study, as described in Section 3.1.

4.4 CONCOMITANT THERAPY

Concomitant therapy includes any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant from 3 months prior to screening to the study completion or discontinuation visit. All such medications (including name, dose, administration schedule, start and end dates) should be reported to the investigator and recorded on the Concomitant Medications eCRF.

4.4.1 Permitted Therapy

Participants are eligible for study participation whether or not they are receiving approved medication for AD (i.e., acetylcholinesterase inhibitors, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who are receiving GV-971 or who are planning to receive GV-971 during the study are not eligible. Information about background AD medication (e.g., drug name, dose, and start and stop dates, reason for interruption or modification) has to be captured on eCRF. Randomization will be stratified for participants taking and not taking approved anti-dementia medications.

Adding a new medication or changing the dose of a medication after randomization should occur only for the treatment of an adverse event or in case of AD progression. Whenever possible, a medication listed below should be used if appropriate.

The following medications are permitted if the dose and dose regimen have been stable for at least 3 months prior to screening and are expected to remain stable after screening or if required for treatment of an adverse event after randomization:

- Anticonvulsant medications for an approved pain indication
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms
- Over-the-counter and/or herbal medications, food additive, or any other agent or supplement intended to improve cognition or reduce cognitive decline
- Medications used to treat a mood or anxiety disorder given as maintenance treatment (with the exception of benzodiazepine)
- Intermittent use of short-acting (non-extended release) opioid medications for pain except within 2 days or 5 half-lives (whichever is the longer) of any cognitive assessment (up to a maximum of 3 consecutive days per month)
- Intermittent use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or a one-time dose of diazepam or a short–acting hypnotic medication (e.g., zolpidem) if use is intermittent for sleep or anxiety, except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the EC or IRB

- Intermittent use of centrally acting antihistamine medications except within 2 days or 5 half-lives (whichever is the longer) prior to any cognitive assessment
- Under certain circumstances, initiation of anti-hemostasis medications during the study conduct

  Anticoagulation therapy lasting no longer than 3 weeks (e.g., temporary usage during surgery) is permitted. Nevertheless, *anticoagulation therapy may require temporary study drug interruption and advice from the Medical Monitor is recommended.*

Concomitant and excluded therapies for determination of participant eligibility are described in Section 4.1.2.7.

Participants who use oral contraceptives, hormone-replacement therapy, or other maintenance therapy should continue their use.

4.4.2 Prohibited Therapy

Any medication that is prohibited before screening is also prohibited during conduct of the study (see Section 4.1.2.7). If a participant receives any prohibited treatment during the study, the participant may be withdrawn from study treatment.

4.5 STUDY ASSESSMENTS

Refer to Appendix 1 for the schedule of activities to be performed during the study.

At applicable sites, certain study assessments may be performed by a home nursing (HN) professional at the participant's home or nursing center to improve access and convenience for participants participating in the study. The Sponsor has selected a healthcare company that is responsible for providing HN services for participating sites (the HN vendor). The HN vendor is responsible for ensuring that all HN professionals are licensed, qualified, and in good standing, as per applicable regulations, and that appropriate background checks have been performed. If the investigator at a participating site determines that HN services are appropriate for a participant and the participant gives written informed consent to participate in HN visits, the HN network communicates with the participant and the participant's site. HN visits are scheduled on specified visit days to allow relevant assessments to be performed by the HN professional. The schedule of activities (see Appendix 1) specifies which assessments may be performed by an HN professional.

4.5.1 Informed Consent Forms and Screening Log

All participants and study partners must review, sign, and date the most current IRB/EC-approved written informed consent for participation in the study before any study-specific prescreening assessments, screening tests or evaluation are performed. Informed Consent Forms for enrolled participants and their study partners and for those who are not subsequently enrolled will be maintained at the study site.

All prescreening and screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before randomization. The investigator will maintain a screening log to record details of all participants prescreened and screened and to confirm eligibility or record reasons for screening failure, as applicable. Prescreening is optional and is covered by a dedicated Informed Consent Form.

4.5.2 Medical History, Concomitant Medication, and Demographic Data

Medical history includes clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), smoking history, use of alcohol, and drugs of abuse. In addition, all medications (e.g., prescription drugs, over-the-counter drugs, herbal or homeopathic remedies, nutritional supplements) used by the participant within 3 months prior to screening visit will be recorded. Demographic data will include age, sex, and self-reported race/ethnicity. Medical history and demographic data will be collected at the screening visit only.

As this study is being conducted in multiple geographic regions, it is likely that participants of different ethnic origins will be enrolled in the study. Although there is currently no indication that gantenerumab is metabolized or eliminated differently or that the treatment effect would be different in participants of different ethnic origins, collecting this information is essential to adequately evaluate the results of this study (e.g., possible differences in PK exposure [concentration of the drug in the blood] or treatment effect).

4.5.3 Physical Examinations

A complete physical examination should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems. Any abnormality identified at baseline should be recorded on the General Medical History and Baseline Conditions eCRF.

The schedule of activities indicates when complete physical examinations (including neurological systems) are to be recorded (see Appendix 1).

Limited, symptom-directed physical examinations should be performed per the schedule of activities (or as clinically indicated). Changes from baseline abnormalities should be recorded in participant notes. New or worsened clinically significant abnormalities should be recorded as adverse events on the Adverse Event eCRF.

In addition, weight will be obtained at screening, and at every visit at which creatinine clearance is tested as well as at any other visit as deemed necessary by the investigator. Height will be obtained at screening only.

4.5.4 Vital Signs

Vital signs will include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements.

Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

Vital sign measurements may be performed by an HN professional.

The schedule of activities indicates when vital signs (blood pressure and pulse rate) are to be recorded (see Appendix 1).

4.5.5 Cognitive, Functional, and Health Economics Assessments

The assessments described in this section will be performed as outlined in the schedule of activities (see Appendix 1) and in the order specified in Section 4.6.

Whenever possible, there should be consistency in the rater and study partner who complete the scales for each participant throughout the duration of the study. Potential raters will receive training and be approved by the rating scale contract research organization (CRO) prior to being allowed to administer any cognitive assessments or rating scales in the study.

Whenever possible, cognitive and functional assessments should be performed at the visit timepoints indicated in the schedule of activities (see Appendix 1). However, in exceptional circumstances for post-randomization visits, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per the schedule of activities, they may be performed up to 4 weeks out of window.

Given that the primary outcome measure in this trial involves subjective judgment, the adequacy of participant and study partner interviews and ratings will be monitored by an endpoint reliability program administered by the rating scale vendor; this is considered an essential part of good research methodology. For the primary endpoint as well as for some other scales, audio recordings may be used for quality assurance purposes. 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 Clinical Dementia Rating Scale

The CDR global score (CDR-GS) characterizes a participant's level of impairment according to the following categories: 0 (normal), 0.5 (very mild dementia), 1 (mild dementia), 2 (moderate dementia), and 3 (severe dementia). The SOB score is a detailed quantitative general index that provides more information than the CDR-GS in

participants with mild dementia (Berg 1988; Morris et al. 2001, O'Bryant et al. 2010) and is scored from 0–18 with higher scores indicating greater impairment. The CDR characterizes six domains: 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 with the participant and a reliable informant or collateral source (e.g., a study partner).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or Alzheimer's Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL). However, if in exceptional circumstances only this assessor is available to perform these other scales, then the CDR participant interview must be completed after the study partner interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, at screening, baseline, Week 104, Week 116 or Week 128 (if applicable), the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should not be involved in safety assessments and especially should not receive information about any ARIA findings.

4.5.5.2 Alzheimer's Disease Assessment Scale–Cognitive Subscale

The ADAS-Cog is the most frequently used scale to assess cognition in clinical trials for mild to moderate AD dementia (Rozzini et al. 2007; Connor and Sabbagh 2008; Ihl et al. 2012). More specifically, the ADAS-Cog is a participant-based assessment that measures learning and memory, language production, language comprehension, constructional praxis, ideational praxis, and orientation. The modified version will be used; it has 13 items and includes the addition of delayed word recall and a number of cancellation subtests, as well as use of only one trial for word recognition (Mohs et al. 1997). Equivalent alternate forms of the word recall, word recognition, and number cancellation subtests will be used in successive test administrations.

4.5.5.3 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 (Folstein et al. 1975). The questions target six areas: orientation, registration, attention, short-term recall, language, and constructional praxis/visuospatial abilities. The MMSE is a participant-based assessment.

4.5.5.4 Free and Cued Selective Reminding Test–Immediate Recall

The FCSRT-Immediate Recall (FCSRT-IR) is a participant-based assessment that measures memory under conditions that control attention and cognitive processing. Impairments in FCSRT-IR performance have been associated with preclinical and early dementia in several longitudinal epidemiological studies (Grober and Buschke 1987; Sarazin et al. 2007). The 16-word version of the test will be used in this study.

4.5.5.5 Verbal Fluency Task

The category verbal fluency (e.g., animals) is a participant-based assessment that measures speed and flexibility of verbal thought. Verbal fluency tests are sensitive tools for detecting dementia (Pasquier et al. 1995; Lezak et al. 2004) and for monitoring decline over time (Clark et al. 2009).

4.5.5.6 Coding

The Coding, also called Digit Symbol Substitution Test (or DSST), is a subtest from the Wechsler Adult Intelligence Scale–Fourth Edition (WAIS–IV; Wechsler 2008). The Coding is a participant-based assessment that measures speed of processing and associative memory. The test is known to be sensitive to disease progression (Lezak et al. 2004). The 120-second version of the test will be used in this study.

4.5.5.7 Functional Activities Questionnaire

The FAQ (Pfeffer et al. 1982) is an informant-based measure of functional abilities. Informants provide performance ratings of the target person on ten complex higher-order activities.

4.5.5.8 Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory

The ADCS-ADL (Galasko et al. 1997) is the scale most widely used to assess functional outcome in participants with AD (Vellas et al. 2008). The ADCS-ADL is a 23-item informant-based questionnaire that covers both basic ADL (e.g., eating and toileting) and more complex ADL or instrumental ADL (e.g., using the telephone, managing finances, preparing a meal). It has a 4-week recall period. Total scores range from 0–78, with higher scores indicating better functioning.

4.5.5.9 Zarit Caregiver Interview–Alzheimer's Disease

The Zarit Caregiver Interview–Alzheimer's Disease (ZCI-AD) is a modified version of the Zarit Burden Interview, which was originally designed to reflect the stresses experienced by caregivers for people with dementia (Zarit and Zarit 1990). The modified version includes slight modifications in item and title wording (e.g., removal of "your relative" to refer directly to the participant, removal of "burden" from title) and the use of 11-point numerical rating scales. The ZCI-AD scale consists of 30 items and is completed by the study partner without involvement from the site staff. It has a 4-week recall period.

4.5.5.10 Quality of Life–Alzheimer's Disease

The Quality of Life–Alzheimer's Disease (QoL-AD) was developed to assess QoL in participants who have dementia (Logsdon et al. 1999, 2002). The QoL-AD consists of 13 items covering aspects of participants' relationships with friends and family, physical condition, mood, concerns about finances, and overall assessment of QoL. The total score is the sum of the 13 items and ranges from 13–52, with higher scores indicating better HRQOL.

In this study, the QoL-AD will be administered in a standardized, structured interview format to participants by investigative staff in order to gather participant responses about QoL. The study partner will also complete the study partner version of the questionnaire to enable proxy responses from the study partner.

4.5.5.11 EQ-5D

The EuroQoL–Five Dimensions (EQ-5D) is a standardized measure of health status designed to provide a simple generic measure of health for clinical and economic appraisal. It is broadly applicable across a wide range of health conditions and treatment.

The EQ-5D assesses five domains to provide a health state index. These are anxiety/depression, pain/discomfort, usual activities, mobility, and self-care.

The following two versions will be used in this study:

- EQ-5D-5L Proxy, Version 1: The study partner (the proxy) is asked to rate the participant's health-related QoL in his or her (the proxy's) opinion.
- EQ-5D-5L, Self-Complete Version: The study partner is asked to rate his or her own health-related QoL.

4.5.5.12 Resource Utilization in Dementia Scale

The Resource Utilization in Dementia (RUD) scale (Wimo et al. 2003) 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 study partner 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, instrumental ADL, 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 recorded 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.

4.5.5.13 Neuropsychiatric Inventory Questionnaire

The Neuropsychiatric Inventory–Questionnaire (NPI-Q) (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in dementia participants, to provide a means of distinguishing severity of behavioral changes, and to facilitate rapid behavioral assessment through the use of screening questions. It is an informant-based instrument in which 12 behavioral domains are evaluated. The recall period is the past month, and severity scores range from 0–36, with higher scores indicating greater severity. The study partner's distress portion of the scale will not be used in this study.

4.5.5.14 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, Verbal Fluency Task, ADCS-ADL, CDR, MMSE, FCSRT, FAQ, AD QoL, EQ-5D, RUD-Lite, NPI-Q, and CSSR-S.

4.5.6 Laboratory, Biomarker, and Other Biological Samples

4.5.6.1 Standard Laboratory Samples

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.

- Serum chemistry: AST, ALT, 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}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed according to the schedule of activities.
- Hematology: hemoglobin, hematocrit, RBC count (with morphology), WBC count, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.
- Screening serology: HIV, hepatitis B, and hepatitis C.
- Coagulation: PT.
- Urine for drugs of abuse: At screening only, urine samples will be analysed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone. Results will be used to verify participant 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 test: Urine pregnancy testing will be performed at each dosing visit (prior to dose administration) 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. If a urine pregnancy test is positive, it must be confirmed by a serum pregnancy test at the central laboratory.

For sampling procedures, storage conditions, and shipment instructions, see the Sample Handling and Logistics Manual.

4.5.6.2 Biomarker Sampling

Samples will be obtained from all participants 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.

For participants who consent to the optional Roche Research Biosample Repository (RBR) residual biomarker samples will be kept for future biomarker research (see Section 4.5.12).

The procedures for the collection, handling, and shipping of biomarker samples are specified in the Sample Handling and Logistic Manual.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (see Section 4.5.12), biomarker samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed. However, the storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Cerebrospinal Fluid and Serum Sampling (for CSF-Enrolled Participants Only)

CSF samples and matching serum samples will be obtained from participants who choose to provide CSF samples during screening (CSF-enrolled participants) for confirmation of Aβ and tau levels for eligibility purposes (mandatory) and for monitoring Aβ and tau levels, as well as other CSF biomarkers at different timepoints during the study. The matching serum samples may be used to determine parameters that allow the assessment of the blood-brain barrier status and/or inflammatory processes in the brain, such as CSF/serum albumin ratio, CSF/serum IgG and IgM indices, and oligoclonal bands. CSF and serum samples will be collected according to the schedule of activities (see Appendix 1). 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 divided into aliquots onsite and used for the following:

- Central measurement of gantenerumab levels in the CSF and biomarker analysis, including $A\beta_{1-42}$, t-tau, p-tau, as well as some exploratory markers. Samples may also be used to support the development of biomarker assays for diagnostic use.

Unused CSF samples will be kept for future biomarker research if the participant gives consent to participate in the RBR (see Section 4.5.12.5).

Clinical Genotyping

During screening, three mandatory 3-mL whole blood samples will be obtained for DNA extraction from every participant who has consented to participate in the study. All participants will be evaluated for *APOE* ε4 status, clusterin (apolipoprotein J) genotypes, 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 and non-response.

APOE ε4 status will be determined and will be blinded to the Sponsor, investigator, and participant and will not be shared with the investigator or the participant until the study is unblinded (unless required for participant safety or by the relevant health authority or IRB/EC). Participants 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, participant *APOE* ε4 status should remain blinded to the site and central MRI readers.

Samples and data may be used for future research or diagnostic test development.

RNA Sampling

During screening and at a subsequent visit as detailed in the schedule of activities (see Appendix 1), two 2.5-mL whole blood samples will be obtained for RNA extraction from every participant who has consented to participate in the study. The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood (see Section 4.5.12).

Plasma Sampling

At screening and at subsequent visits as detailed in the schedule of activities (see Appendix 1), two 6-mL whole blood sample will be obtained for plasma extraction from every participant who has consented to participate in the study.

This sample will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, $p\text{-}Tau,\ and$ neurofilament.

An additional plasma sample for the assessment of exploratory plasma biomarkers will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes

aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

4.5.6.3 Anti-Drug Antibody Sampling

Blood samples will be collected to assess the possible development of ADAs in all participants as noted in the schedule of activities (see Appendix 1). Plasma samples will be analysed for antibodies to gantenerumab using a bridging ELISA.

Samples collected from participants 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.

The procedures for the collection, handling, and shipping of ADA samples are specified in the Sample Handling and Logistics Manual supplied to the site.

4.5.6.4 Pharmacokinetic Sampling

Plasma Gantenerumab Samples

Blood samples will be collected to evaluate the pharmacokinetics of gantenerumab in plasma as noted in the schedule of activities (see Appendix 1).

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) once the site becomes aware of the occurrence or worsening of ARIA-E, or occurrence of ARIA-H meeting discontinuation criteria.

Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate. Samples will not be analysed in real time but will be batched for analysis throughout the study.

Unused sample material may be used for the purpose of current gantenerumab assay improvement, for the quantification of specific gantenerumab glycan species, and for the assessment of exploratory plasma biomarkers.

The procedures for the collection, handling, and shipping of PK samples are specified in the Sample Handling and Logistics Manual supplied to the site.

Cerebral Spinal Fluid for Assessment of Gantenerumab Concentration (for Participants Enrolled on the Basis of CSF Criteria Only)

For participants enrolled on the basis of CSF criteria and willing to perform lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.6.2, will be allocated for the measurement of gantenerumab concentration. Samples from participants receiving placebo may not be assessed at once but will be retained for subsequent analysis if appropriate.

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

4.5.7 Electrocardiograms

Single 12-lead ECG recordings will be obtained at specified timepoints, as outlined in the schedule of activities (see Appendix 1), and may be obtained at unscheduled timepoints as indicated.

All ECG recordings must be performed using a standard high-quality, high-fidelity digital electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the participant's permanent study file at the site.

The centrally provided electrocardiograph machine should record the following: heart rate, QRS duration, and RR, PR, and QT intervals and transferred to the Sponsor database from the core laboratory.

4.5.8 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 participant (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 or potential lethality. The C-SSRS baseline will be collected at baseline and the C-SSRS since the last visit will be collected at subsequent visits as indicated in the schedule of activities (see Appendix 1).

The assessment will be completed by a certified C-SSRS rater after he or she interviews the participant and the participant’s study partner during the study visit.

4.5.9 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners, and wherever possible the same scanner should be used for an individual participant for the full duration of the study. MRI will be conducted at participant screening for safety monitoring, as a baseline measure of structural brain volumes, and as baseline information for the PET substudies (for the schedule of activities, see Appendix 1).

Where available, exploratory MRI techniques including rs-fMRI and DTI will also be acquired. 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).

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 performed to better understand relevant CNS adverse events (such as increased confusion) occurring in the context of ARIA or to follow a sign that emerges at a scheduled scan; contrast agent may be used in such a case of follow-up MRI scans if administration of contrast agent is considered safe for the participant according to local standards. In addition, structural MRI (to assess whole brain and regional brain atrophy), fMRI, and DTI-MRI will be performed at multiple timepoints to determine potential treatment effects on MRI outcome measures (according to the schedule of activities).

MRI scans will include the following sequences:

- 3D T_1-weighted gradient recalled echo (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 and sequences)
- DTI-MRI, if available (to assess fiber tract integrity)

For details on the specific imaging sequences and acquisition times required, refer to the MRI Manual.

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.

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

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 (refer to Section 5.1.2 for additional details on MRI safety management).

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

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

4.5.10 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 participant is scanned in this study. The choice of healthy volunteers is at the discretion of the 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 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, any other event deemed significant enough to affect image quality, or per central reader guidance. 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.

Additional instructions regarding the procedures for MRI facility qualification can be found in the MRI Manual.

4.5.11 Positron Emission Tomography Scan

A PET scan will be performed for confirmation of Aβ levels for eligibility purposes in participants (PET-enrolled participants). Three radioligands are be used for screening purposes: [^{18}F] florbetapir (Amyvid™), [^{18}F] flutemetamol (Vizamyl™), and [^{18}F] florbetaben (Neuraceq™).

Screening PET scans must not be acquired prior, potentially exclusionary screening results are available in order to minimize radiation burden to participants. In order to allow sufficient flexibility for scheduling of the screening PET scan screening procedures (including central reading of the MRI scans) ideally should be completed within 2–3 weeks before the screening PET scan is required.

A positive PET scan using [^{18}F] florbetapir, [^{18}F] flutemetamol, or [^{18}F] florbetaben acquired outside this study protocol may be permissible to confirm participant inclusion with Medical Monitor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Detailed instructions regarding the procedures for PET scan methodology, including scanning procedures can be found in the PET Technical Operations Manual.

4.5.12 Optional Samples for Research Biosample Repository

4.5.12.1 Overview of the Research Biosample Repository

The RBR 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, storage, and analysis of RBR specimens will facilitate the rational design of new pharmaceutical agents and the development of diagnostic tests, which may allow for individualized drug therapy for participants in the future.

Specimens for the RBR will be retained from participants who give specific consent to participate in this optional research.

RBR 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

4.5.12.2 Approval by the Institutional Review Board or Ethics Committee

Collection and submission of biological samples to the RBR is contingent upon the review and approval of the exploratory research and the RBR portion of the Informed Consent Form by each site's IRB/EC and, if applicable, an appropriate regulatory body. If a site has not been granted approval for RBR sampling, this section of the protocol (Section 4.5.12) will not be applicable at that site.

4.5.12.3 Sample Collection

The following samples will be stored in the RBR and used for research purposes, including, but not limited to, research on biomarkers related to gantenerumab or AD:

- Leftover blood from Clinical Genotyping sample and clinical RNA sample and any derivatives thereof (e.g., DNA, RNA, proteins, peptides), plasma biomarker sample, CSF samples, and serum samples

The above samples may be sent to one or more laboratories for analysis of germline or somatic mutations via whole genome sequencing (WGS), whole exome sequencing (WES), next-generation sequencing, or other genomic analysis methods.

Genomics is increasingly informing researcher's understanding of disease pathobiology. WGS and WES provide a comprehensive characterization of the genome and exome, respectively, and, along with clinical data collected in this study, may increase the opportunity for developing new therapeutic approaches. Data will be analysed in the context of this study but will also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification of important pathways, guiding the development of new targeted agents.

For sampling procedures, storage conditions, and shipment instructions, see the laboratory manual.

RBR specimens are to be stored until they are no longer needed or until they are exhausted. However, the RBR storage period will be in accordance with the IRB/EC-approved Informed Consent Form and applicable laws (e.g., health authority requirements).

4.5.12.4 Confidentiality

Specimens and associated data will be labeled with a unique participant identification number.

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

Given the complexity and exploratory nature of the analyses of RBR specimens, data derived from these analyses will generally not be provided to study investigators or participants unless required by law. The aggregate results of any conducted research will be available in accordance with the effective Sponsor policy on study data publication.

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

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

4.5.12.5 Consent to Participate in the Research Biosample Repository

The Informed Consent Form will contain a separate section that addresses participation in the RBR. The investigator or authorized designee will explain to each participant the objectives, methods, and potential hazards of participation in the RBR. Participants 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 participant's agreement to provide optional RBR specimens. Participants who decline to participate will not provide a separate signature.

The investigator should document whether or not the participant has given consent to participate and (if applicable) the date(s) of consent, by completing the RBR Research Sample Informed Consent eCRF.

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

4.5.12.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR specimens have the right to withdraw their specimens from the RBR at any time for any reason. If a participant wishes to withdraw consent to the testing of his or her specimens, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and, if the trial is ongoing, must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. The participant will be provided with instructions on how to withdraw consent after the trial is closed. A participant's withdrawal from Study WN29922 does not, by itself, constitute withdrawal of specimens from the RBR. Likewise, a participant's withdrawal from the RBR does not constitute withdrawal from Study WN29922.

4.5.12.7 Monitoring and Oversight

RBR 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. Sponsor monitors and auditors will have direct access to appropriate parts of records relating to participant participation in the RBR for the purposes of verifying the data provided to the Sponsor. 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 RBR samples.

4.6 TIMING OF STUDY ASSESSMENTS

4.6.1 Screening and Pretreatment Assessments

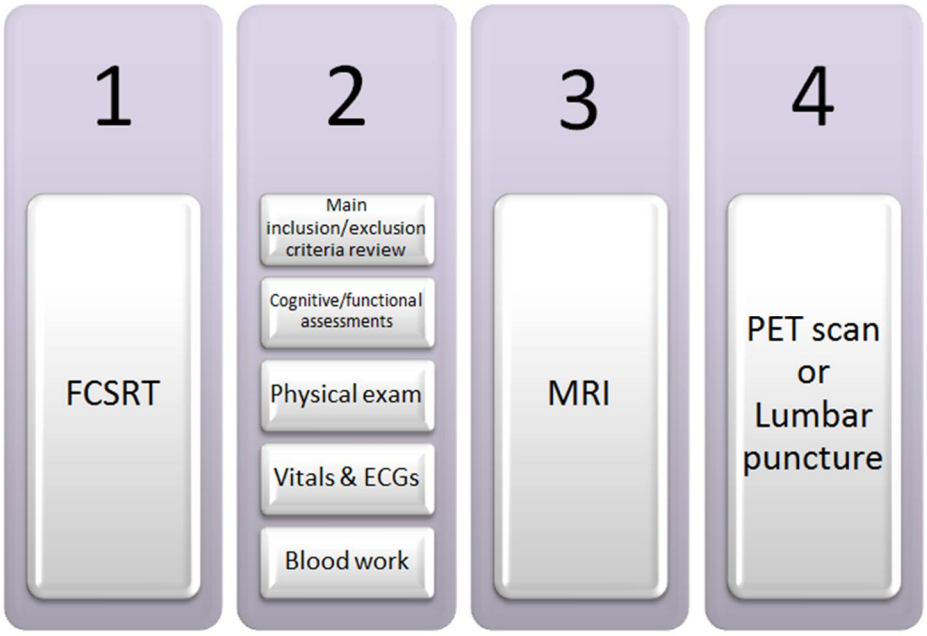
Written informed consent for participation in the study must be obtained before performing any study-specific screening tests or evaluations. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site. After providing written informed consent, participants who are willing to participate in the study will undergo all screening assessments within 12 weeks prior to the baseline visit, as detailed in the schedule of activities (see Appendix 1). Participants must fulfill all the entry criteria for participation in the study and the results must be available prior to the baseline visit.

The FCSRT and MMSE assessments may also be completed at prescreening. However, in this case, a separate prescreening consent would need to be signed and FCSRT and MMSE would not need to be repeated during the screening process. In case the participant would not qualify based on the FCSRT inclusion criteria, investigators have the option to repeat the FCSRT once after at least 6 months have elapsed if recruitment for the study is still ongoing. Rescreening of participants who failed MMSE is not allowed.

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 12-week screening window) once to confirm the test results before randomizing a participant at baseline.

In rare cases in which an MRI scan needs to be repeated or any other unexpected delay due to logistical or technical reasons, the screening period may be extended by some days. Extending the screening period beyond 12 weeks must be approved by the Medical Monitor and should be for exceptional circumstances only; careful scheduling should remain a priority.

The recommended order of screening assessments is as follows:



ECG = electrocardiogram; FCSRT = Free and Cued Selective Reminding Test; MRI = magnetic resonance imaging; PET = positron emission tomography.

The recommended order of clinical assessments and rating scales at screening is shown below.

Participant Assessments	Study Partner Assessments
1. FCSRT (performed at prescreening or at screening) 10-min break (optional) 2. MMSE (performed at prescreening or at screening) 3. CDR (participant interview)	CDR (study partner input)

CDR = Clinical Dementia Rating; FCSRT = Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination.

CSF sampling, PET scan, and MRI scan at screening should be performed only once all other screening results are available and none exclude the participant from the trial.

If a participant does not qualify on the basis of applicable tests, the participant may be rescreened again after at least 3 months (6 months for FCSRT) have elapsed if recruitment for the study is still ongoing.

As noted in the exclusion criteria (see Section 4.1.2), participants may be rescreened after appropriate treatment if they were originally excluded for abnormal thyroid, folic acid, vitamin B-12, or HbA_{1c} results. Other laboratory tests that would exclude the participant may be repeated once (as an unscheduled laboratory assessment) if it is suspected that the abnormal result is transient and likely to be normal on repeat.

Participants 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 with the exception of lumbar puncture (if performed within the previous 12 months for this study and within eligible ranges) and PET scan within eligible ranges. Given that *APOE* status will not change over time, there is no need to repeat clinical genotyping in case of rescreening.

Participants may be rescreened if there is a substantial change in the participant's condition (e.g., a disallowed medication was stopped) and if recruitment for the study is still ongoing and all eligibility criteria are met.

It is suggested that screening tests with the exception of the lumbar puncture, MRI scan, and PET scan be performed within 1 to 2 weeks of signing the Informed Consent Form (to allow adequate time for the remaining tests). As soon as all the results are available, and none exclude the participant from the trial, CSF collection and/or PET scan and MRI scan should be performed, if required.

It will take several days to receive the results of the MRI or CSF. 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 participants enrolling on the basis of PET criteria, and for participants willing to participate in any of the PET substudies, scans can be obtained after all other screening results are available. For these participants, it is recommended that the MRI appointment should be scheduled to allow sufficient time for the PET scan to be performed and evaluated before the end of the screening period.

A positive PET scan using Amyvid™, Vizamyl™, or Neuraceq™ acquired outside this study may be permissible to confirm participant inclusion with Sponsor approval. Previously acquired PET scans must meet quality standards detailed in the PET Technical Operations Manual and must be centrally evaluated.

Roche may keep information about screening test results, medical history, and demographic information for all participants (including non-eligible participants) for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

4.6.2 Assessments at Baseline

In order to be randomized and to receive double-blind treatment, participants must have no significant change in medical, psychiatric, or neurological conditions or change in medication since screening. The recommended order of assessments and rating scales is as follows:

- Clinical assessments (e.g., CDR, MMSE, and ADAS-Cog), including all those that require study partner input, should be completed before any invasive safety assessments.
- Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, and plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must all be performed prior to study drug administration.

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

Participant Assessments	Study Partner Assessments
1. ADAS-Cog13	1. CDR (study partner input)
2. CDR (participant interview)	2. FAQ
10-min break (optional)	3. ADCS-ADL
3. MMSE	4. ZCI-AD
4. Coding	5. QoL-AD
5. Verbal Fluency Task	6. EQ-5D
10-min break (optional)	7. RUD-Lite
6. QoL-AD	8. NPI-Q
7. C-SSRS	

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study-Activities of Daily Living; CDR = Clinical Dementia Rating; C-SSRS = Columbia–Suicide Severity Rating Scale; EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; NPI-Q = Neuropsychiatric Inventory–Questionnaire; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

If assessments are split over 2 days, all safety assessments must be performed on the same day as the study drug administration.

4.6.3 Assessments during the Double-Blind Treatment Period

In the double-blind treatment period, participants will receive up to 49 (in scenario 1) or 55 (in scenario 2, if applicable) SC administrations of study drug over the course of 114 or 126 (if applicable) weeks, respectively. The final on-treatment efficacy and safety assessments are scheduled 2 weeks after the last dose. Participants who have completed the double-blind treatment period at the time of the implementation of *the study extension by 12 weeks,* received up to 43 doses and underwent the final efficacy and safety assessments at Week 104, 2 weeks after the last dose.

The same recommended order of clinical assessments and rating scales as above for the baseline visit should be followed (omitting those that are not conducted per the schedule of activities; see Appendix 1). *However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.*

Vital sign measurements, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples are *must be performed prior to study drug administration. They are also* recommended to be conducted following scale assessments.

If assessments are split over 2 days, all safety assessments must be done on same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab or matching placebo will be administered subcutaneously at room temperature. For the first four doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., Doses 5 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

Visits at which the participant receives study drug may take place within ±7 days of the protocol-specified date for Q4W administration and ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Always return to initial planned schedule per randomization for subsequent visits.

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 performed 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 and rating scales for the participant have been completed.

For sites and participants 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 performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1 for the schedule of activities during the treatment period.

4.6.4 Assessments during Open-Label Extension Period

The same recommended order of clinical assessments and rating scales as in the double-blind treatment period (see Appendix 1), as well as vital sign measurements,

ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarkers, and urine samples *must be performed prior to study drug administration. They are also* are recommended to be conducted following scale assessments. If assessments are split over 2 days, all safety assessments must be performed on the same day as the treatment administration.

On each dosing day, after all assessments prior to dosing have been completed (see Appendix 1), gantenerumab and/or matching placebo will be administered subcutaneously at room temperature. For the first eight doses, participants should be observed for a minimum of 2 hours after dosing and then for a minimum of 1 hour after all remaining doses (i.e., doses 9 and beyond). Participants should leave the study center after injections only if they appear to be tolerating the injections. When doses are to be administered remotely from the clinical sites, study drug administration may be performed only by qualified health care providers, as defined by local regulations, who must remain with the participants for a minimum of 1 hour after each injection and be equipped with rescue medications.

Rescue medications to treat anaphylactic and anaphylactoid reactions must be available at the site or at the dosing location for HN visits. Participants and their study partners will be alerted to watch for signs of anaphylactic and anaphylactoid reactions and to contact the study center as soon as possible if any such signs are noted.

In the OLE, visits at which the participant receives study drug may take place ±3 days of the protocol-specified date for Q2W administration per the schedule of activities in Appendix 1. Always return to the initial planned schedule per randomization for subsequent visits.

For sites and participants 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 performed at an alternate location conducted by appropriate health care professionals.

Refer to Appendix 1, Table 3 for the schedule of activities during the OLE.

4.6.5 Procedures for New MRI Findings

In addition to any local reading according to 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 participant eligibility as well as for analysis, results from the expert central reader 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 (see Section 4.5.9).

Refer to Section 5.1.2 for instructions in the event of new MRI findings (ARIA-E and ARIA-H).

4.6.6 Assessments at Study Completion or Early Termination Visit

Participants who complete the double-blind treatment period at Week 114 in scenario 1 or at Week 126 in scenario 2 (if applicable) will have to complete the final efficacy and safety assessment period 2 weeks following the last dose. Some participants may have already received the last study drug administration at Week 102 and performed the final efficacy and safety visit at Week 104 at the time of implementation of *the study extension by 12 weeks.*

All participants will be asked to come back for the follow-up assessments 14 weeks and 50 weeks after the last dose, unless they are transitioning to an OLE.

All participants who withdraw from treatment or discontinue from the study early (during the double-blind treatment period or during the OLE) will be asked to return 2 weeks after the last dose of study drug in order to complete the early termination visit.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments per the schedule of activities until the end of the double-blind treatment period or until the last OLE follow-up visit (OLE Follow up 2) for those who enrolled in the OLE period.

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the Week 50 follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion in Appendix 1.

4.6.7 Follow-Up Assessments

Participants who complete the double-blind treatment period and who are not willing to enroll in an OLE or these who complete the OLE period (defined as administration of at least three 510-mg doses Q4W) and are not willing to enroll in the WN42171 open-label study will be asked to return to the clinic 14 weeks and 50 weeks after the last dose of study drug for the follow-up visits (Follow Up 1 and Follow Up 2 or OLE Follow Up 1 and OLE Follow Up 2, respectively)..

When participants 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 or early termination visit, adverse events should be followed as outlined in Sections 5.5 and 5.7. Refer to the schedule of activities (see Appendix 1) for the list of assessments to be performed at the follow-up visits.

4.6.8 Unscheduled Assessments

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 activities in Appendix 1 allows for all assessments to be performed at unscheduled visits.

4.7 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.7.1 Study Treatment Discontinuation

Participants must discontinue study treatment if they experience any of the following:

- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Investigator or Sponsor determines it is in the best interest of the participant
- Pregnancy
- Upon evidence of more than 15 ARIA-H, cumulatively
- Any disseminated leptomeningeal hemosiderosis

All participants who withdraw from treatment will be asked to return 2 weeks after last dose in order to complete the early termination visit assessments.

In addition, participants who withdraw from treatment will be asked to return for collection of safety (except MRI) and limited efficacy data (i.e., the primary and secondary endpoints) at visits that have efficacy assessments according to the schedule of activities until the end of the double-blind treatment period, *and then the follow-up visits*, or until the last OLE follow-up visit (OLE Follow Up 2) for those who enrolled in the OLE.

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

4.7.2 Participant Discontinuation

Participants have the right to voluntarily withdraw from the study at any time for any reason. In addition, the investigator has the right to withdraw a participant from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Participant withdrawal of consent at any time
- Study termination or site closure
- Any medical condition that the investigator *and* Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Investigator or Sponsor determines it is in the best interest of the participant

- Participant non-compliance with the study and/or study procedures, defined as missing more than three consecutive dose administrations (with Q4W dosing regimen) or more than six consecutive dose administrations (with Q2W dosing regimen) because of non–safety-related reasons or more than half of the dosing visits in a calendar year

All participants who discontinue from the study early will be asked to return 2 weeks after last dose in order to complete the early termination visit.

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

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

Participants who withdraw from the study will not be replaced.

4.7.3 Study 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 participants.
- Participant enrollment is unsatisfactory.
- Futility analyses suggesting that treatment with gantenerumab is likely not effective.
- Sponsor determines it is the best interest of the participants.

The Sponsor will notify the investigator if the Sponsor decides to discontinue the study.

4.7.4 Site Discontinuation

The Sponsor has the right to close a site at any time. Reasons for closing 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 Council for Harmonisation (ICH) guideline for Good Clinical Practice
- No study activity (i.e., all participants have completed the study 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 participants in this study is based on clinical experience with gantenerumab in completed and ongoing studies. The identified risks for gantenerumab are outlined below. Please refer to the Gantenerumab Investigator's Brochure for a complete summary of safety information.

Several measures will be taken to ensure the safety of participants enrolled in this study. Eligibility criteria have been designed to exclude participants at higher risk for imaging-related abnormalities. Participants will undergo safety monitoring during the study, including assessment of the nature, frequency, and severity of adverse events. In addition, guidelines for managing adverse events, including criteria for dosage modification and treatment interruption or discontinuation, are provided below.

5.1.1 Risks Associated with Gantenerumab

5.1.1.1 Amyloid-Related Imaging Abnormalities

To date, clinical experience with gantenerumab reveals that ARIA events are dose-dependent and *APOE* ε4 dependent. These events are manageable with MRI monitoring and dose intervention algorithms. In addition, in case of clinical symptoms, the use of IV glucorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 6.

5.1.1.2 Injection-Site Reactions

Gantenerumab may cause a reaction when given as an SC injection. In studies with gantenerumab, the most common events occurring more frequently with gantenerumab than with placebo were local ISRs, such as injection-site erythema. The majority of events were of mild intensity and resolved without treatment (see Section 1.2.3 for details).

Detailed information on the characteristic signs and symptoms of ISRs (e.g., erythema, pruritus) will be recorded on the dedicated eCRF page (see Section 5.3.5.2 for details on recording of ISRs).

5.1.1.3 Immunogenicity

As with administration of any exogenous protein, there is the potential for the development of ADAs, which can be neutralizing and/or sensitizing and which can potentially lead to febrile or allergic reactions, including anaphylaxis. The immunogenic risk of gantenerumab is considered low since it is a fully human antibody.

There are no clinical findings indicative of an immunogenic response to gantenerumab. Participants should be told how to recognize the signs and symptoms of hypersensitivity reactions and be monitored.

5.1.2 Management of Participants Who Experience Selected Adverse Events

Participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans) and according to the schedule of activities once the target dose is achieved. The pre-uptitration MRI scans will determine eligibility for the next uptitration dose. In the double-blind treatment period, a minimum of 3 doses of each dosing step have to be administered before the participant is eligible for the next uptitration dose. In the OLE, a minimum of 3 doses of each dosing step must be administered prior to be eligible for uptitration. In the OLE, a dose is defined as two consecutive dosing visits (one with an even dose number and one with an odd dose number, see Table 4, Section 4.3.2.2).

Participants will be eligible for uptitration if there are no new ARIA-E, if the ARIA-E is resolved (BGTS=0), and if the criteria for discontinuation because of ARIA-H have not been met.

In addition, the following dose adjustment and discontinuation rules for MRI 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 uptitrate) and repeat MRI 4 weeks later.

  As long as BGTS is <4 and ≥1, continue study drug at the same dose level and continue MRI monitoring at 4-week intervals until the event resolves. When ARIA-E resolves, resume uptitration and MRI monitoring according to the schedule of activities.

  If BGTS ≥4 or symptoms develop, refer to the rule below.

- In case of occurrence of symptoms in the presence of ARIA-E (any size) or asymptomatic ARIA-E with ≥4 BGTS: Temporarily interrupt study drug (but continue all assessments per schedule of activities) and implement MRI monitoring performed at 4-week intervals until symptoms and ARIA resolve.

  When symptoms and ARIA-E resolve, reintroduce study drug at the next scheduled dosing visit, at the same dose given at the time the event was detected and perform an MRI scan after the first dose for participants on Q4W regimen and after the second dose for participants on the Q2W regimen.

  If no new ARIA-E is detected, resume uptitration and obtain an MRI scan per the titration schedule. For participants on the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.

- In exceptional cases of 1) an ARIA-E that is asymptomatic with BGTS <4 and that is considered stable over consecutive MRI images by the Sponsor and investigator; or 2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but

the CNS symptoms continue, the study drug can either be reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

- Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings.
- Any recurrence of ARIA-E: Treat using the same procedures as for the first event (based on symptoms and BGTS).
- Participants who develop $>$15 ARIA-H cumulatively will be discontinued from study drug (the cumulative number should not include any disseminated leptomeningeal hemosiderosis, i.e., up to 3 focal leptomeningeal hemosiderosis *either on the same scan or cumulatively*; a focal leptomeningeal hemosiderosis is counted as an ARIA-H).
- In cases where both ARIA-E and ARIA-H occur, the most conservative approach should be followed.
- A PK sample and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meet the discontinuation criteria.
- The investigators may choose to perform additional MRI monitoring for ARIA at any time.
- MRI monitoring of ARIA findings should be conducted at approximately 4-week intervals.
- Any other new significant findings will be reviewed by the medical monitor and appropriate dose action will be taken.

The iDMC reviews the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management for the overall study population or for a specific *APOE* ε4 genotype.

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:

- Is fatal (i.e., the adverse event actually causes or leads to death)
- Is life threatening (i.e., the adverse event, in the view of the investigator, places the participant 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 5.3.5.12)
- Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
- Is a congenital anomaly/birth defect in a neonate/infant born to a mother exposed to study drug
- Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant 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 (e.g., rated as mild, moderate, or severe; 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 5.3.5.8)
- Suspected transmission of an infectious agent by the study drug, as defined below

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

5.2.4 Selected Adverse Events

Data on associated symptoms 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/or hemosiderin deposits

Please refer also to Section 5.3.5.1 for further details how to report ARIA events.

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). The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact. All adverse events, whether reported by the participant, the study partner, or noted by study

personnel, will be recorded in the participant'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).

In addition, after administration of a PET ligand, but prior to initiation of study drug, the following adverse events should be reported:

- All adverse events (serious or non-serious) believed to be related to a PET ligand
- All serious adverse events occurring within 48 hours of PET ligand administration regardless of relatedness to the PET ligand

For reporting of serious adverse events, see Section 5.4.2 for instructions. For non-serious PET ligand adverse events, a PET ligand specific non-serious adverse event reporting paper form should be completed and submitted to the Sponsor or its designee by scanning and emailing the form using the email address provided on the form.

After initiation of study drug, all adverse events will be reported until the participant's last visit (including long-term follow-up visits).

Instructions for reporting adverse events that occur after the adverse event reporting period are provided in 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 participant 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 5 provides guidance for assessing adverse event severity.

Table 5 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 should use their knowledge of the participant, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether an adverse event is considered to be 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, with special consideration of the effects of dose reduction, discontinuation of study drug, or reintroduction of study drug (as 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 participant 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

5.3.5 Procedures for Recording Adverse Events

Investigators 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 ARIA Findings

Not every ARIA finding qualifies as an adverse event. An ARIA finding must be reported as an adverse event if it meets any of the following criteria:

- Symptomatic ARIA-E (i.e., accompanied by CNS symptoms), and/or
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation), and/or

- Findings that are otherwise clinically significant in the investigator's judgment.

Any accompanying symptoms should also be captured as separate adverse events.

It is the investigator's responsibility to review all ARIA findings.

Observations of the same clinically significant ARIA finding should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.2 Injection Reactions

Injection reactions (local and systemic) are defined as adverse events that occur during or within 24 hours after study drug administration that are judged to be related to the study drug injection.

For local reactions, the diagnosis of injection site reaction should be captured on the Adverse Event eCRF, and associated signs and symptoms (e.g., erythema at injection site) should be recorded on the dedicated Injection Site Reaction eCRF.

Systemic reactions should be recorded as a single diagnosis on the Adverse Event eCRF (e.g., anaphylactic reaction). If possible, avoid ambiguous terms such as "systemic reaction."

5.3.5.3 Diagnosis versus Signs and Symptoms

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.

5.3.5.4 Adverse Events That Are Secondary to Other Events

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

- If vomiting results in mild dehydration with no additional treatment in a healthy adult, only vomiting should be reported on the eCRF.
- If vomiting results in severe dehydration, both events should be reported separately on the eCRF.

- If a severe gastrointestinal hemorrhage leads to renal failure, both events should be reported separately on the eCRF.
- If dizziness leads to a fall and consequent fracture, all three events should be reported separately on the eCRF.
- If neutropenia is accompanied by an infection, both events should be reported separately on the eCRF.

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

5.3.5.5 Persistent or Recurrent Adverse Events

A persistent adverse event is one that extends continuously, without resolution, between participant evaluation timepoints. Such events should only be recorded once on the Adverse Event eCRF. The initial severity (intensity or grade) of the event will be recorded at the time the event is first reported. If a persistent adverse event becomes more severe, the most extreme severity should also be recorded on the Adverse Event eCRF. If the event becomes serious, it should be 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 Adverse Event eCRF should be updated by changing the event from “non-serious” to “serious,” providing the date that the event became serious, and completing all data fields related to serious adverse events.

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

5.3.5.6 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., dosage modification, treatment interruption, or treatment discontinuation)
- Results in a medical intervention (e.g., potassium supplementation for hypokalemia) or a change in concomitant therapy
- Is 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× ULN associated with cholestasis), only the diagnosis (i.e., cholestasis) should be recorded on the Adverse Event eCRF.

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

Observations of the same clinically significant laboratory abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.7 Abnormal Vital Sign Values

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

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

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

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

Observations of the same clinically significant vital sign abnormality from visit to visit should only be recorded once on the Adverse Event eCRF (see Section 5.3.5.5 for details on recording persistent adverse events).

5.3.5.8 Abnormal Liver Function Tests

The finding of an elevated ALT or AST ($>3\times$ULN) in combination with either an elevated total bilirubin ($>2\times$ULN) or clinical jaundice in the absence of cholestasis or other causes of hyperbilirubinemia is considered to be an indicator of severe liver injury (as defined by Hy’s Law). Therefore, investigators must report as an adverse event 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).

5.3.5.9 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 (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.

Deaths that occur after the adverse event reporting period should be reported as described in Section 5.6.

5.3.5.10 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").

5.3.5.11 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. If there is any uncertainty as to whether an event is because of disease progression, it should be reported as an adverse event.

5.3.5.12 Hospitalization or Prolonged Hospitalization

Any adverse event that results in hospitalization (i.e., inpatient admission to a hospital) or prolonged hospitalization should be documented and reported as a serious adverse event (per the definition of serious adverse event in 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
- Hospitalization due to expected progression of underlying disease
- 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 all 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 participant has not experienced an adverse event

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

An overdose is the accidental or intentional use of a study drug in an amount higher than the dose being studied. An overdose or incorrect administration of 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 seriousness 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).

5.3.5.14 Clinical Outcome Assessment Data

Adverse event reports will not be derived from clinical outcome assessment (COA) data by the Sponsor, and safety analyses will not be performed using COA data. Sites are not expected to review the COA data for adverse events.

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 (defined in Section 5.2.2; see Section 5.4.2 for details on reporting requirements)
- Adverse events of special interest (defined in Section 5.2.3; see Section 5.4.2 for details on reporting requirements)
- Pregnancies (see Section 5.4.3 for details on reporting requirements)
- Medical device complaints (see Section 5.4.4 for details on reporting requirements)

For serious adverse events and adverse events of special interest, the investigator must report new significant follow-up information 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 Contact Information

Medical Monitor: [redacted], *MBBS, PhD* (Primary)

Mobile Telephone No.: [redacted]

Medical Monitor: [redacted], *M.D., MSc* (Secondary)

Mobile Telephone No.: [redacted]

To ensure the safety of study participants, 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 Responsible (listed above and/or on the Roche Medical Emergency List), 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, as well as Medical Monitor and Medical Responsible contact information, will be distributed to all investigators.

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

5.4.2.1 Events That Occur prior to Study Drug Initiation

After informed consent has been obtained but prior to initiation of study drug, only serious adverse events caused by a protocol-mandated intervention should be reported.

In addition, the following serious adverse events should be reported after administration of a PET ligand and prior to initiation of study drug:

- All serious adverse events believed to be related to the PET ligand
- All serious adverse events occurring within 48 hours of the PET ligand administration, regardless of relatedness to the PET ligand.

The paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators.

5.4.2.2 Events That Occur after Study Drug Initiation

After initiation of study drug, serious adverse events and adverse events of special interest will be reported until the participant's last visit (including long-term follow-up visits). Investigators should record all case details that can be gathered immediately (i.e., within 24 hours after learning of the event) 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, the paper Serious Adverse Event/Adverse Event of Special Interest Reporting Form provided to investigators should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the event), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Once the EDC system is available, all information will need to be entered and submitted via the EDC system.

Instructions for reporting serious adverse events that occur after the adverse event reporting period are provided in Section 5.6.

5.4.3 Reporting Requirements for Pregnancies

5.4.3.1 Pregnancies in Female Participants

Female participants 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 paper Clinical Trial Pregnancy Reporting Form should be completed and submitted to the Sponsor or its designee immediately (i.e., no more than 24 hours after learning of the pregnancy), either by faxing or by scanning and emailing the form using the fax number or email address provided to investigators. Pregnancy should not be recorded on the Adverse Event eCRF. The investigator should discontinue study drug and counsel the participant, discussing the risks of the pregnancy and the possible effects on the fetus. Monitoring of the participant 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 addition, the investigator will submit a Clinical Trial Pregnancy Reporting Form when updated information on the course and outcome of the pregnancy becomes available.

5.4.3.2 Abortions

A spontaneous abortion should be classified as a serious adverse event (as the Sponsor considers abortions to be medically significant), 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).

If a therapeutic or elective abortion was performed because of an underlying maternal or embryofetal toxicity, the toxicity 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). A therapeutic or elective abortion performed for reasons other than an underlying maternal or embryofetal toxicity is not considered an adverse event.

All abortions should be reported as pregnancy outcomes on the paper Clinical Trial Pregnancy Reporting Form.

5.4.3.3 Congenital Anomalies/Birth Defects

Any congenital anomaly/birth defect in a child born to a female participant exposed to study drug 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

The investigator must report all medical device complaints (e.g., devices for study drug administration) to the Sponsor. The investigator should document as much information as possible on the IMP Deviation Form, including the product batch number, and forward

the form to the Sponsor immediately (i.e., no more than 24 hours after learning of the event) (refer to the pharmacy manual for further details). If the medical device results in an adverse event to the study participant, the event must be reported on the Adverse Event eCRF and submitted through the EDC system. If the event is serious, the Adverse Event eCRF must be completed immediately (i.e., no more than 24 hours after learning of the event), as outlined in Section 5.4.2.

5.5 FOLLOW-UP OF PARTICIPANTS 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 participant is lost to follow-up, or the participant 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 participant's medical record to facilitate source data verification.

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

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, email, and/or a monitoring visit to obtain additional case details and outcome information (e.g., from hospital discharge summaries, consultant reports, autopsy reports) in order to perform an independent medical assessment of the reported case.

5.6 ADVERSE EVENTS THAT OCCUR AFTER THE ADVERSE EVENT REPORTING PERIOD

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 the participant's last study visit), if the event is believed to be related to prior study drug treatment. These events should be reported through use of the Adverse Event eCRF. However, if the EDC system is not available, the investigator should report these events directly to the Sponsor or its designee, either by faxing or by scanning and emailing the paper Clinical Trial Serious Adverse Event/Adverse Event of Special Interest Reporting Form using the fax number or email address provided to 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 these events using the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
[^{18}F] Florbetaben (Neuraceq™)	[^{18}F] Florbetaben Investigator's Brochure
[^{18}F] Flutemetamol (Vizamyl™)	[^{18}F] Flutemetamol Investigator's Brochure
[^{18}F] Florbetapir (Amyvid™)	[^{18}F] Florbetapir Investigator's Brochure
[^{18}F] GTP1	[^{18}F] GTP1 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

The purpose of this study is to investigate the treatment effect of gantenerumab relative to placebo. The primary efficacy analysis will be based on an intent-to-treat (ITT) population, which will include all randomized participants during the global enrollment phase, with participants grouped according to their randomly assigned treatment.

Approximately 1016 participants will be randomized in the global enrollment phase of this study. An increase in sample size may be considered in case of changes to sample size assumptions based on blinded data review or factors external to the study.

If at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase, additional participants may be enrolled in a China extension to ensure a total enrollment that is sufficient to support registration in the China.

The primary analyses of this study will include participants enrolled during the global enrollment phase; data from participants enrolled during the China extension will not be included in the primary analyses.

Details of the planned statistical analyses mentioned below will be fully specified in a separate SAP, which will be finalized prior to the locking and unblinding of the study database.

6.1 DETERMINATION OF SAMPLE SIZE

Determination of sample size is based on participants enrolled in the global enrollment phase. In this study, approximately 1016 participants will be enrolled and randomized in 1:1 ratio to each treatment arm (gantenerumab or placebo) during the global enrollment phase. A sample size increase may be considered if factors external to the study or blinded study data review would warrant a change to the sample size assumptions.

Additional participants may be randomized during the China extension if at least 1 participant is enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA during the global enrollment phase.

The estimated sample size required to demonstrate efficacy with regard to CDR-SOB is based on the following assumptions:

- The mean change in the CDR-SOB from baseline to Week 104 is 2.5 points in the placebo arm
- A common standard deviation across treatment arms for change of approximately 2.97 from baseline to Week 104 in the CDR-SOB
- Gantenerumab has a true effect of a 30% relative reduction in deterioration of CDR-SOB

Based on these assumptions, and using a student's T-test with equal variance, a sample size was calculated for 90% power to detect a true treatment effect of 30% relative reduction in deterioration of CDR-SOB at a two-sided α of 0.05.

Uncertainties on parameters affecting the power (e.g., dropout rate, study drug discontinuation rate, standard deviation, and placebo decline) were assumed to be equivalent to a drop-in sample size of up to around 35% and were corrected for accordingly. This calculation leads to a total of 1016 participants in the study.

At the date of writing Protocol Version 4, it is expected that participants *would have* miss*ed* an average of 8 weeks of study drug administration over the course of the original 2-year study due to the COVID-19 pandemic. This has the potential to decrease the power of the study from ~90% to ~80%. To mitigate the impact of missed administrations, the double-blind treatment period *was* extended by 12 weeks. Under current assumptions, this brings the study power back to the originally planned ~90%.

The sample size may be increased from 1016 up to 1322 participants (661 participants per arm). The decision whether to increase sample size will be based on blinded study data review, e.g., by a review of the frequency of missed study drug administrations due to the COVID-19 pandemic. Further details will be described in the SAP. The

assessment will be performed by the Sponsor at a specified timepoint. The sponsor will remain blinded. The sample size will not be reduced on the basis of this assessment. Other factors external to the study may also trigger a decision to increase sample size.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized for the ITT population according to the randomly assigned treatment arms.

6.3 SUMMARIES OF TREATMENT GROUP COMPARABILITY

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, use, and non-use of background therapy for AD) will be summarized descriptively for the ITT population, grouped according to the assigned treatment arm.

Descriptive summaries of continuous data will present the mean, standard deviation, median, and minimum and maximum. Descriptive summaries of discrete data will include frequencies expressed in terms of number and percentage of participants.

6.4 EFFICACY ANALYSES

The primary and secondary efficacy analyses will use the ITT population, with participants grouped according to the treatment assigned at randomization.

6.4.1 Primary Efficacy Endpoint

The primary efficacy outcome measure is the change in CDR-SOB from baseline (Day 1) to Week 116. In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The clinical question of interest is to assess the study treatment effect on disease progression up to Week 116 (or Week 128, if applicable), irrespective of use or initiation of symptomatic treatments for AD, in the absence of the COVID-19 pandemic.

In accordance with the estimand framework outlined in the ICH-E9 addendum (EMA 2018), the attributes of the estimand for the primary endpoint are defined as follows:

- *Population: early (prodromal to mild) AD population including all randomized participants.*
- *Variable: change from baseline at Week 116 (or Week 128) in the CDR-SOB*
    - *Treatment: prescribed study drug including uptitration to the target dose, irrespective of use or initiation of symptomatic treatment for AD.*
- *Intercurrent events (ICE): the list of ICE will be defined in the SAP, this includes:*
    - *Treatment discontinued for study drug or condition–related (SDCR) reasons (e.g., treatment-related adverse event or lack of efficacy):*

- *Treatment discontinued for non-SDCR (NSDCR) reasons (e.g. purely administrative reason)*

- *Population level summary: mean change from baseline to Week 116 (or Week 128, as appropriate) between gantenerumab-treated participants and placebo-treated participants.*

The primary estimand is a combination of a treatment-policy strategy and a hypothetical strategy (FDA 2017) to account for the different assumptions for each type of ICE, SDCR or NSDCR.

Full details of the primary estimand, and of the corresponding estimator and estimation methods (e.g. statistical model, multiple imputation for missing or excluded data points) will be provided in the SAP. Supplementary estimands may also be considered and will be defined in the SAP.

Every effort will be made to minimize missing data. Furthermore, the Sponsor *has made* every effort to expedite the implementation of *the 12 week extension to the double-blind treatment period*. If the study is extended by an additional 12 weeks (for a total extension of 24 weeks), the number of patients in scenario 1 (who will have missing Week 128 efficacy data) will be minimized.

Participants who discontinue early from study treatment will be asked to return for collection of safety and limited efficacy data (i.e., the primary and secondary efficacy endpoints) until the end of the double-blind treatment period and follow-up visits.

Descriptive summaries of the number of participants with missing data, the number of participants in each scenario, the timing, and reasons for discontinuation from the study will also be provided by treatment group.

Additional details will be documented in the SAP.

6.4.2 Secondary Efficacy Endpoints

The absolute change from baseline in the continuous secondary efficacy endpoints listed in Section 2, Table 2 (including cognition/function endpoints, global endpoints, disease pathology biomarkers, and endpoints measuring other AD symptoms and effects) will be analysed using *an approach* similar to that described above for the primary efficacy endpoint.

In order to protect the overall type I error rate for the study when incorporating the hypothesis testing of the primary endpoint and secondary endpoints into the analysis, the fixed sequence testing procedure (Westfall and Krishen 2001) will be used to adjust for multiple comparisons. The first endpoint that will be tested is:

- Change from baseline to Week 116 in CDR-SOB

In the case where the double-blind treatment period is extended for an additional 12 weeks, the primary efficacy outcome measure will be the change in CDR-SOB from baseline (Day 1) to Week 128.

The order of testing for other secondary endpoints will be defined in the SAP.

The treatment difference in the primary endpoint (the change from baseline to Week 116 in the CDR-SOB) will be tested at a two-sided 5% overall significance level. If this test result is statistically significant, the secondary endpoints will be tested for significance in the predefined order as specified in the SAP. If any test result is not statistically significant, testing of the subsequent endpoints will not occur.

6.4.3 Exploratory Efficacy Analyses

Subgroup analysis of efficacy results will be performed for subgroups defined by age, sex, race, stage of disease (prodromal AD vs. mild AD), *APOE* ε4 status, geographic region, use and non-use of background therapies for AD, and other clinically relevant factors at baseline.

The efficacy endpoints collected during the Study WN29922 open-label treatment phase and during Study WN42171 *may* be combined with data from the Study WN29922 double-blind treatment phase in order to evaluate change from baseline beyond the end of the double-blind treatment period and to evaluate the effect of a delayed start of treatment with gantenerumab.

6.4.4 Pharmacodynamic and Exploratory Biomarker Analyses

PD and exploratory biomarker endpoints will be analysed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured endpoints, the change from baseline and the difference between participants randomized to gantenerumab and participants randomized to placebo will be estimated if appropriate.

Prior to completion of the study a separate PD cutoff date may be established to allow expedient sample analyses and early access by third party vendors.

Exploratory biomarkers may be reported separately.

6.5 SAFETY ANALYSES

The safety-analysis population will include all randomized participants who receive at least one dose of study drug, with participants grouped according to the treatment actually received, as defined in the SAP.

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

- Incidence of adverse events of special interest
- Incidence of treatment discontinuations due to adverse events
- Mean changes in clinical laboratory tests from baseline over time; incidence of treatment-emergent abnormal laboratory values and abnormal laboratory values reported as adverse events
- Mean change in ECG assessments from baseline over time and incidence of abnormal ECG assessments
- Physical and neurologic examination abnormalities
- Mean change in vital signs (blood pressure, pulse rate) from baseline over time and incidence of abnormal vital sign measurements
- Changes in CSSR-S scores from baseline over time
- Number and proportion of participants with ADAs during the study relative to the number and proportion of participants with ADAs at baseline

Prior to completion of the study a separate ADA cutoff date may be established to allow expedient samples analyses and early access by third party vendors. The ADA cutoff date will be applied when there is sufficient ADA sample data available to adequately assess immunogenicity.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab *may* be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, SD, and coefficient of variation, as appropriate. Because a sparse PK sampling design is being used, population (non-linear mixed-effects) modeling will be used to analyse the dose concentration–time data of gantenerumab. Information from other clinical studies may be incorporated to establish the PK model. The selection of parameters and the derivation of individual measures of exposure, such as AUC, C_{max}, and trough serum concentration, will depend on the final PK model used for this analysis. 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.

The results of this modeling analysis may be reported separately from the clinical study report.

CSF concentrations of gantenerumab *may* be tabulated and summarized as appropriate.

Prior to completion of the study a separate PK cutoff date may be established to allow expedient sample analyses and early access by third party vendors. The PK cutoff date will be applied when there is sufficient PK sample data available to adequately characterize PK.

Additional PK analyses will be conducted as appropriate and may be reported separately from the clinical study report.

6.7 INTERIM ANALYSIS

6.7.1 *Optional Futility Analysis*

*Sponsor may perform a*n interim analysis for futility approximately 116 weeks after 50% of the targeted study enrollment has been reached. If the study is extended by an additional 12 weeks, the interim analysis will be performed approximately 128 weeks after 50% of the targeted study enrollment has been reached. The exact timing of an interim analysis may be synchronized with Study WN39658.

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC *and the Sponsor will remain blinded. Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may recommend stop for futility if the failure criterion is met. The failure criterion will represent a low probability of a positive study outcome given the data observed at the time of interim analysis. *If the futility criteria are not met, the study continues beyond the interim analysis. The failure criterion will be pre-specified in the iSAP.*

Details of the futility analysis, including the final decision to conduct it, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and futility thresholds) will be documented in the iSAP. This will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.7.2 Optional Interim Analyses

Based on availability of information pertaining to gantenerumab or other compounds with similar mode of action that may emerge during the course of this study, the Sponsor may choose to conduct an additional interim analysis *which may include efficacy, safety and biomarker outcomes including amyloid PET SUVr and/or other biomarkers to confirm PD effect. This analysis may be done on a whole study population or in a well predefined subgroup when approximately 50% of the overall population has reached Week 116. If the study is extended by an additional 12 weeks, the interim analysis will be performed once approximately 50% of the overall population has reached Week 128.*

An independent data coordinating center will be responsible for the interim analyses. The study results will only be reviewed by the iDMC *and th*e Sponsor will remain blinded. *Other third party vendors may be involved in data preparation and analyses, as appropriate.*

The iDMC may indicate that a pre-specified success criterion has been met. If so, the Sponsor may decide to present the data to a health authority. Any interim, unblinded data will be strictly firewalled to ensure those involved in the conduct of the ongoing trial and the WN42171 OLE trial remain fully blinded. If needed, appropriate measures will be taken to control the overall Type I error rate and described in the SAP

Details of the interim analyses, including the decision to conduct the optional interim analyses, the rationale, timing, and statistical details for the analyses (such as the data that would be reviewed by the iDMC and efficacy thresholds) will be documented in an iSAP, and the iSAP will be submitted to relevant health authorities at least 2 months prior to the conduct of the interim analysis.

6.8 CHINA EXTENSION ANALYSIS

The objective of the China extension and the China subpopulation analyses is to assess the treatment effects of gantenerumab in a population of participants enrolled at sites in mainland China, Hong Kong, and Taiwan that are recognized by the NMPA and to investigate the consistency in treatment effect between the China subpopulation and the global population for the purpose of registration in China.

All participants enrolled in the global enrollment phase in China will be included in the primary analysis. The analysis of the China extension will be conducted after the end of China extension and will be reported separately from the primary analysis and at a subsequent point in time. Details will be provided in the SAP.

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 through use of 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.

COA data will be collected through the use of an electronic device (tablet) provided by a vendor. Some COA data may be audio recorded for quality assurance purposes. The

device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with U.S. FDA regulations for electronic records (21 CFR, Part 11). The electronic data are available for view access only via 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. The Sponsor will have view access only. System backups for data stored by the Sponsor and records retention for the study data will be consistent with the Sponsor's standard procedures.

7.2 ELECTRONIC CASE REPORT FORMS

eCRFs are to be completed through use of 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 participant 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 CLINICAL OUTCOME DATA

Participants, study partners, and appropriate site staff will use an electronic device (tablet) to capture COA. For some COA, audio recordings may be used for quality assurance purposes. All data will be transmitted via Web automatically after entry into a centralized database maintained by the electronic device vendor.

Once the study is complete, the data, audit trail, and trial and system documentation will be archived. The investigator will receive participant 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 data in a machine-readable format on a compact disc.

7.4 SOURCE DATA DOCUMENTATION

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

Source documents (paper or electronic) are those in which participant 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, participant-reported outcomes, 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, participant 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 into the eCRFs (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 into 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 study site must also allow inspection by applicable health authorities.

7.5 USE OF COMPUTERIZED SYSTEMS

When clinical observations are entered directly into a study 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, 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, electronic COA data, Informed Consent Forms, laboratory test results, and medication 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 European Union or European Economic Area will comply with the E.U. 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 a Child's Informed Assent Form or Home Nursing Informed Consent Form, if applicable) 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.

If applicable, the Informed Consent Form will contain separate sections for any optional procedures. The investigator or authorized designee will explain to each participant the objectives, methods, and potential risks associated with each optional procedure. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time for any reason. A separate, specific signature will be required to document a participant's agreement to participate in optional procedures. Participants who decline to participate will not provide a separate signature.

The Consent Forms must be signed and dated by the participant or the participant's legally authorized representative before his or her participation in the study. The case history or clinical records for each participant shall document the informed consent process and that written informed consent was obtained prior to participation in the study.

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 participant to participate. The final revised IRB/EC-approved Consent Forms must be provided to the Sponsor for health authority submission purposes.

Participants must be re-consented to the most current version of the Consent Forms (or to a significant new information/findings addendum in accordance with applicable laws and IRB/EC policy) during their participation in the study. For any updated or revised Consent Forms, the case history or clinical records for each participant 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.

A copy of each signed Consent Form must be provided to the participant or the participant's legally authorized representative. All signed and dated Consent Forms must remain in each participant'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 participant 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 participant 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 participant, 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 participant 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 participant enrolled in the study through assignment of a unique participant identification number. This means

that participant names are not included in data sets that are transmitted to any Sponsor location.

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

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

Data generated by this study must be available for inspection upon request by representatives of 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., LPLV).

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 participant data, including 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 have an impact on participant 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, subjects' 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.

Study drug distribution may occur through an IxRS (see Section 4.2). Central facilities may be used for study assessments (i.e., ECG, lumbar puncture, specified laboratory tests, PK, rating scales, and MRI and PET imaging, as applicable).

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 participants 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 participants 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.

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 participants or changes that involve logistical or administrative aspects only (e.g., change in Medical Monitor or contact information).

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Appendix 1
Schedule of Activities

Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Informed consent(s) [c]	x											
Review of inclusion and exclusion criteria	x	B										
Medical history, personal status, and demographics	x											
Weight and height [t]	x	x							x			x
Clinical genotyping samples	x											
Clinical RNA samples	x											
Urinalysis [d]	x											
Urine sample for drugs of abuse [e]	x											
Coagulation (PT)	x											
Viral serology (HIV, hepatitis B, and hepatitis C)	x											
FCSRT	P [f]											
12-Lead electrocardiogram [g]	x	B				B			B			x
PK plasma sample [h, v]		B	x						B			x
ADA sample		B							B			x
Serum chemistry [i] and hematology [j]	x	B							B			x
Plasma biomarker sample [u]	x								B			x
Complete physical examination (includes neurological systems) [k]	x											x

Appendix 1: Schedule of Activities (cont.)
Table 1: Week –12 to Week 32; Dose Escalation with Q4W Administration (cont.)

Assessment/Procedure	Prescreen & Screening	Baseline	Dose Escalation Period									Unsched Visit
	Weeks –12 to –1	Day 1	Day 4	Wk 4	Wk 8	Wk 12	Wk 16	Wk 20	Wk 24	Wk 28	Wk 32	
Dose Number		1 [a]		2	3	4	5 [b]	6 [b]	7 [a]	8 [b]	9 [b]	
Dose level in milligrams (mg)		120		120	120	255	255	255	510	510	510	
Limited physical examination [l]									B			x
MRI scan [m, n]	x [o]					B			B			x
CSF and matching serum sampling [m, p] or PET scan [m, p]	x											
CDR	P&SP	P&SP							P&SP			P&SP
ADAS-Cog13		P							P			P
Verbal Fluency Task		P							P			P
Coding		P							P			P
ADCS-ADL		SP							SP			SP
FAQ		SP							SP			SP
MMSE	P [f]	P							P			P
EQ-5D		SP							SP			SP
QoL-AD		P&SP							P&SP			P&SP
ZCI-AD		SP							SP			SP
RUD-Lite		SP							SP			SP
NPI-Q		SP							SP			SP
C-SSRS BL/SLV		P							P			P
Vital signs [q]	x	B	B	B	B	B	B	B	B	B	B	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [r]	x	B		B	B	B	B	B	B	B	B	x
Study drug administration [h, s]		x		x	x	x	x	x	x	x	x	

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; Prescreen=prescreening; Q4W=every 4 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner completion.

Notes: The visit window is ±7 days for dosing days and +3 days for non-dosing Day 4. For Q4W injections, the recommended minimum time between doses is 3 weeks. The maximum recommended time between doses should not exceed 6 weeks. Participants should return to initial planned schedule per randomization for subsequent visits.

In case of rescreening a participant, all screening assessments must be repeated other than the lumbar puncture and amyloid PET testing if performed within the previous 12 months for this study and are within the eligible ranges. In addition, clinical genotyping will not need to be repeated in case of rescreening.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first, and within 1 week prior to the first dose at baseline. All safety assessments (e.g., vital signs, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, for post-randomization visits, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Participants in the optional prescreening period must provide written consent before any study-specific prescreening assessments are performed. If participant is eligible and decides to participate in the screening assessments, he or she will need to provide new written consent.

[d] Performed at the site by dipstick for blood, protein, glucose, and pH.

[e] Urine samples will be analysed for the presence of the following drugs: amphetamine, benzodiazepines, cannabinoids, opiates, cocaine, barbiturates, and methadone.

[f] Can be done at prescreening or at screening. There is no need to repeat the test at screening if performed at prescreening.

[g] Electrocardiograph machine equipped with computer-based interval measurements. Lead placement should be as consistent as possible. ECG recordings must be performed after the participant has been resting in a supine position for at least 5 minutes. All ECGs are to be obtained prior to other procedures scheduled at that same time (e.g., vital sign measurements, blood draws, brain MRI scans, and lumbar puncture). Circumstances that may induce changes in heart rate, including environmental distractions (e.g., television, radio, conversation), should be avoided during the pre-ECG resting period and during ECG recording.

[h] Accurate recording of the date and time of study drug administration and PK sampling is critical.

[i] Serum chemistry includes AST, ALT, 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 –12), hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[j] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelets, basophils, eosinophils, lymphocytes, monocytes, neutrophils, and WBC–other total counts.

[k] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[l] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[m] CSF and matching serum sampling, and PET and MRI scans at screening should be performed once all other screening results are available and none exclude the participant from the study.

[n] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. It is not recommended that the MRI be performed on the same day as the IMP administration (especially during uptitration period during which it is recommended to do the MRI at least 10 days after the third dose of sing step). MRI should be performed before or at least 3 days following a lumbar puncture.

[o] Includes resting-state functional MRI and DTI outcome measures where available.

[p] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters. For post-baseline visits, lumbar puncture as well as serum sampling should be performed prior to dosing. Only one method (CSF or PET) confirming amyloid is necessary for all participants.

[q] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[r] 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. Results are to be recorded only in the source documents.

[s] Study drug administration should be performed only after all assessments/rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by SC injection. Participants should be observed up to 2 hours after dosing. After the fourth injection visit, the observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[t] Height measured at screening only.

[u] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[v] A plasma PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 2: Week 36 to the End of Study: 510 mg Q2W

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
12-Lead ECG						B		B			x	x		x	x
PK plasma sample [d]				x (Site visit)		B		B		x (Site visit)		x	x	x	x
ADA sample						B		B				x	x	x	x
Clinical RNA sample											x			x	
Serum chemistry [e] and hematology [f]						B		B			x	x	x	x	x
Plasma biomarker sample [o]						B					x			x	x
Complete physical examination (including neurological systems) [g]											x			x	x
Limited physical examination [h]						B		B							x
Weight						x		x			x	x	x	x	x

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
MRI scan [i]	B				Wk 48 [j]		Wk 60	B			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)								x			x			x [k]	
CDR						P&SP		P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13						P		P			P		P	P	P
Verbal Fluency Task						P		P			P		P	P	P
Coding						P		P			P		P	P	P
ADCS-ADL						SP		SP			SP		SP	SP	SP
FAQ						SP		SP			SP		SP	SP	SP
MMSE						P		P			P		P	P	P
EQ-5D						SP		SP			SP			SP	SP
QoL-AD						P&SP		P&SP			P&SP			P&SP	P&SP
ZCI-AD						SP		SP			SP			SP	SP
RUD-Lite						SP		SP			SP			SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

												Only for Participants Who Have Completed Week 104 when *the 12 week study extension* is Implemented			
	Treatment Period										Final Efficacy and Safety Assessments	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
Assessment/Procedure	Wk 36	Wk 38	Wk 40	Wk 41	Wk 42–50	Wk 52	Wk 54–74	Wk 76	Wk 78–102	Wk 103	Wk 104 [a, b]	Wk 116	Wk 152		
Dose number	10	11	12		13–17 [c]	18 [a]	19–29 [c]	30 [a]	31–43 [c]						
Dose level in milligrams (mg)	510	510	510		510	510	510	510	510						
NPI-Q						SP		SP			SP			SP	SP
C-SSRS BL/SLV						P		P			P			P	P
Vital signs [l]	B	B	B		B	B	B	B	B		x	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [m]	B	B	B		B	B	B	B	B		x	x		x	x
Study drug administration [d, n]	x	x	x		x	x	x	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL=Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR=Clinical Dementia Rating; CSF=cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D=EuroQol-Five Dimensions; FAQ=Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE=Mini-Mental State Examination; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET=positron emission tomography; PK=pharmacokinetic; Q2W=every 2 weeks; QoL-AD=Quality of Life–Alzheimer's Disease; RBR=Research Biosample Repository; RUD-Lite=Resource Utilization in Dementia–Lite; SC=subcutaneous; Unsched=unscheduled; Wk=week; ZCI-AD=Zarit Caregiver Interview–Alzheimer's Disease.

B=before study drug administration; P=participant completion; P&SP=participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 2: Week 36 to the End of Study: 510 mg Q2W (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for Week 41 and Week 103 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, 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 52 and Week 104, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary (optional), and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76. Lumbar puncture does not have to be performed the same day as the main Week 76 visit or Week 104 visit, but should be performed in a reasonable time around these visits. The need for CSF collection at early termination visit will be discussed on a case-by-case *based on the participant's condition and the time since last lumbar puncture and advice by the Medical Monitor may be sought.*

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[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. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the fourth injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 1
Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W

(3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104 [a]	Wk 106-114 [c]	Wk 115	Wk 116 [a, b]	Wk 128	Wk 164		
Dose number	44	45-49						
Dose level in milligrams (mg)	510	510						
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QoL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

Appendix 1: Schedule of Activities (cont.)

Table 3: Scenario 1 / Week 104 to the End of Study: 510 mg Q2W (3-Month Extension)

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL =Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR =Clinical Dementia Rating; CSF =cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D =EuroQol-Five Dimensions; FAQ =Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET =positron emission tomography; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life–Alzheimer's Disease; RBR =Research Biosample Repository; RUD-Lite =Resource Utilization in Dementia–Lite; SC =subcutaneous; Unsched =unscheduled; Wk =week; ZCI-AD =Zarit Caregiver Interview–Alzheimer's Disease.

B =before study drug administration; P =participant completion; P&SP=participant and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days and +3 days for Week 115 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week –12 to Week 103 for scenario 1 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[e] Serum chemistry includes AST, ALT, 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 and Week 116, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76 ; lumbar

puncture does not have to be performed the day of Week 76 or Week 116 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should be determined on a case-by-case basis based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[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. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 4: Scenario 2 / Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
12-Lead ECG	x			x	x		x	x
PK plasma sample [d]			x (site visit)		x	x	x	x
ADA sample					x	x	x	x
Clinical RNA sample	x			x			x	
Serum chemistry [e] and hematology [f]	x			x	x	x	x	x
Plasma biomarker sample [o]	x			x			x	x
Complete physical examination (including neurological systems) [g]				x			x	x
Limited physical examination [h]	x							x
Weight	x			x	x	x	x	x
MRI scan [i]	x [j]			x [j]			x [j]	x
CSF [k] and matching serum sampling (for participants enrolled based on CSF eligibility criteria only)				x			x [k]	
CDR	P&SP			P&SP		P&SP	P&SP	P&SP
ADAS-Cog13	P			P		P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

Assessment/Procedure	Treatment Period			Final Safety and Efficacy Assessment	Follow-Up Period for Participants Not Enrolling in the OLE		Early Term Visit [a]	Unsched Visit
	Wk 104[a]	Wk 106-126[c]	Wk 127	Wk 128[a, b]	Wk 140	Wk 176		
Dose number	44	45-55						
Dose level in milligrams (mg)	510	510						
Verbal Fluency Task	P			P		P	P	P
Coding	P			P		P	P	P
ADCS-ADL	SP			SP		SP	SP	SP
FAQ	SP			SP		SP	SP	SP
MMSE	P			P		P	P	P
EQ-5D	SP			SP			SP	SP
QoL-AD	P&SP			P&SP			P&SP	P&SP
ZCI-AD	SP			SP			SP	SP
RUD-Lite	SP			SP			SP	SP
NPI-Q	SP			SP			SP	SP
C-SSRS BL/SLV	P			P			P	P
Vital signs [l]	x	x		x	x	x	x	x
Concomitant medications	x	x		x	x	x	x	x
Adverse events	x	x		x	x	x	x	x
Urine pregnancy test [m]	x	x		x	x		x	x
Study drug administration [d, n]	x	x						

ADAS-Cog13=Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL =Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR =Clinical Dementia Rating; CSF =cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D =EuroQol-Five Dimensions; FAQ =Functional Activities Questionnaire; FCSRT=Free and Cued Selective Reminding Test; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET =positron emission tomography; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life–Alzheimer's Disease; RBR =Research Biosample Repository; RUD-Lite =Resource Utilization in Dementia–Lite; SC =subcutaneous; Unsched =unscheduled; Wk =week; ZCI-AD =Zarit Caregiver Interview–Alzheimer's Disease.

Appendix 1: Schedule of Activities (cont.)
Table 4: Scenario 2 Only Week 104 to the End of Study: 510 mg Q2W (Additional 3-Month Extension)

B =before study drug administration; P =participant completion; P&SP=participant and study partner completion; SP=study partner.

Notes: The visit window is ±3 days for dosing days and +3 days for Week 127 non-dosing days. For Q2W injections, the recommendation is not to administer more than 1020 mg (i.e., 2 times 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

SoA from Week –12 to Week 103 for scenario 2 is described in Appendix 1, Table 1 and Table 2.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater, or even the participant cannot perform these assessments as per schedule of activities, they may be performed up to 4 weeks out of window.

[b] Transition to OLE study for participants who are eligible to participate.

[c] Visit suitable for home administration of gantenerumab.

[d] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[e] Serum chemistry includes AST, ALT, 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 and Week 128, hemoglobin A_{1C}, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[f] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[g] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[j] Includes resting-state functional MRI and DTI outcome measures, where available.

[k] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, CSF and matching serum samples are optional at Week 76; lumbar puncture does not have to be performed the day of Week 76 or Week 128 visit, but should be performed in a reasonable time around these visits; the need of CSF collection at early termination visit *should be determined on a case-by-case basis based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[l] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[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. Results are to be recorded only in the source documents.

[n] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for about 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[o] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

Appendix 1
Schedule of Activities (cont.)

Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9[b]	10[b]	11[b]	12[b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Informed consent(s)	x														
Review of inclusion and exclusion criteria	x														
Weight														x	x
12-Lead electrocardiogram								B						x	x
PK Plasma Sample [c]	x	x												x	x
ADA sample	x													x	x
Serum chemistry [d] and hematology [e]														x	x

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9[b]	10[b]	11[b]	12[b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
Plasma biomarker sample [l]														x	x
Complete physical examination (includes neurological systems) [f]														x	x
Limited physical examination [g]															x
MRI scan [h]								B						x [n]	x
CDR														P&SP	P&SP
ADAS-Cog 13														P	P
MMSE														P	P
Verbal Fluency Test														P	P
Coding														P	P
ADCS-ADL														SP	SP
FAQ														SP	SP
EQ-5D														SP	SP
QoL-AD														P&SP	P&SP
ZCI-AD														SP	SP

Appendix 1: Schedule of Activities (cont.)
Table 5: Schedule of Activities (OLE Day 1 to Week 22: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period													OLE Early Term Visit [m]	OLE UV
	OLE Day 1	OLE Day 4	OLE Wk 2	OLE Wk 4	OLE Wk 6	OLE Wk 8	OLE Wk 10	OLE Wk 12	OLE Wk 14	OLE Wk 16	OLE Wk 18	OLE Wk 20	OLE Wk 22		
Dose number	1[a]		2	3	4	5	6	7	8	9 [b]	10 [b]	11 [b]	12 [b]		
Dose level in milligrams (mg) for participants previously on placebo	120			120		120		255		255		255			
Dose level in milligrams (mg) for participants previously on active	510		510	510	510	510	510	510	510	510	510	510	510		
RUD-Lite														SP	SP
NPI-Q														SP	SP
C-SSRS/SLV														P	P
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)														x [o]	
Vital Signs [i]	B	x	B	B	B	B	B	B	B	B	B	B	B	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [i]	B		B	B	B	B	B	B	B	B	B	B	B	x	x
Study drug administration [c, k]	x		x	x	x	x	x	x	x	x	x	x	x		

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission

tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; UV = unscheduled visit; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] OLE Day 1 dosing should take place approximately 2 weeks after final efficacy visit has been completed.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[d] Serum chemistry includes AST, ALT, 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 early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[j] 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. Results are to be recorded only in the source documents.

[k] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[l] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria

[m] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[n] Includes resting-state functional MRI and DTI outcome measures, where available.

[o] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For patients enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should be determined* on a case-by-case basis *based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

Appendix 1
Schedule of Activities (cont.)

Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
Informed consent(s)											
Review of inclusion and exclusion criteria											
Weight	x							x	x	x	x
12-Lead electrocardiogram	x							x		x	x
PK plasma sample [c]	x							x	x	*x*	*x*
ADA sample	x							x	x	x	x
Serum chemistry [d] and hematology [e]	x							x	x	x	x
Plasma biomarker sample [n]	x									x	x
Complete physical examination (includes neurological systems) [f]										x	x
Limited physical examination [g]	x										x

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
MRI scan [h]	B						x			x[i]	x
CDR	P&SP								P&SP	P&SP	P&SP
ADAS-Cog 13	P								P	P	P
MMSE	P								P	P	P
Verbal Fluency Test	P								P	P	P
Coding	P								P	P	P
ADCS-ADL	SP								SP	SP	SP
FAQ	SP								SP	SP	SP
EQ-5D	SP								SP	SP	SP
QoL-AD	P&SP								P&SP	P&SP	P&SP
ZCI-AD	SP								SP	SP	SP
RUD-Lite	SP								SP	SP	SP
NPI-Q	SP								SP	SP	SP
C-SSRS/SLV	P								P	P	P

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Assessment/Procedure	Open-Label Extension Treatment Period							Follow-up Period for Participants Not Enrolling in Study WN42171		OLE Early Term Visit [a]	OLE Unsched Visit
	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34	OLE Wk 35	OLE Follow Up 1	OLE Follow Up 2		
Dose number	13 [a]	14 [b]	15 [b]	16 [b]	17 [b]	18 [b]					
Dose level in milligrams (mg) for participants previously on placebo	510		510		510						
Dose level in milligrams (mg) for participants previously on active	510	510	510	510	510	510					
CSF and matching serum sampling (for participants enrolled based on CSF eligibility criteria in double-blind part only)										x [j]	
Vital signs [k]	B	B	B	B	B	B		x	x	x	x
Concomitant medications	x	x	x	x	x	x		x	x	x	x
Adverse events	x	x	x	x	x	x		x	x	x	x
Urine pregnancy test [l]	B	B	B	B	B	B		x		x	x
Study drug administration [c, m]	x	x	x	x	x	x					

ADAS-Cog13= Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; CDR = Clinical Dementia Rating; CSF = cerebral spinal fluid; C-SSRS=Columbia–Suicide Severity Rating Scale; DTI=diffusion tensor imaging; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FCSRT= Free and Cued Selective Reminding Test; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory–Questionnaire; OLE=open-label extension; PET = positron emission tomography; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RBR = Research Biosample Repository; RUD-Lite = Resource Utilization in Dementia–Lite; SC = subcutaneous; Unsched = unscheduled; Wk = week; ZCI-AD = Zarit Caregiver Interview–Alzheimer's Disease.

B = before study drug administration; P = participant completion; P&SP= participant and study partner completion; SP=study partner.

Appendix 1: Schedule of Activities (cont.)
Table 6: Schedule of Activities (OLE Week 24 to Week 35: Dose Escalation with Q2W Administration) (cont.)

Notes: The visit window is ± 3 days for dosing days and +3 days for OLE non-dosing Day 4. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. All safety assessments (e.g., vitals, blood tests, and ECGs) should be completed on the day of dosing. Whenever possible, cognitive and functional assessments should be performed at the visit timepoints stipulated in the schedule of activities. However, in exceptional circumstances, if the caregiver, the primary rater or even the participant cannot perform these assessments as per schedule of activities they may be performed up to 4 weeks out of window.

[b] Visit suitable for home administration of gantenerumab.

[c] Accurate recording of the date and time of study drug administration and PK sampling is critical. A PK sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

[d] Serum chemistry includes AST, ALT, 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 early termination, hemoglobin A1C, glucose, insulin, total cholesterol, HDL, LDL, triglycerides, C-reactive protein, folic acid, vitamin B-12, T4, free T4, and thyroid-stimulating hormone levels will also be assessed and should ideally be collected at least 4 hours after meals.

[e] Hematology includes hemoglobin, hematocrit, RBC count (with morphology), WBC counts, platelet, basophil, eosinophil, lymphocyte, monocyte, neutrophil, and WBC–other total counts.

[f] A complete physical examination includes an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, genitourinary, and neurological systems.

[g] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[h] MRI must be performed at least 7 days before dosing and results must be available for review by site staff before dosing can proceed. MRI should be performed before or at least 3 days following a lumbar puncture.

[i] Includes resting-state functional MRI and DTI outcome measures, where available.

[j] Lumbar puncture must be performed in the morning (between 8:00 a.m. and noon) to minimize potential diurnal variation of CSF parameters and should be performed prior to dosing. For participants enrolling based on CSF eligibility criteria, the need of CSF collection at early termination visit during OLE *should be determined* on a case-by-case basis *based on the participant's condition and the time since last lumbar puncture and advice from* the Medical Monitor may be sought.

[k] Vital signs include measurements of pulse rate and systolic and diastolic blood pressure. Blood pressure and pulse rate should be taken when the participant is at rest and should not be measured unless at least 15 minutes have elapsed since the last blood draw. The same arm should be used for all blood pressure measurements. Pulse rate will be determined and will be recorded as beats per minute. If obtained manually, the pulse rate should be counted for a minimum of 20 seconds at each assessment.

[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. Results are to be recorded only in the source documents.

[m] Study drug administration should be performed only after all assessments and rating scales for the participant are completed (unless indicated otherwise). Study drug will be administered to participants by subcutaneous injection (full details are provided in the pharmacy manual). Participants should be observed for up to 2 hours after dosing. After the 8th injection visit, this observation time may be reduced to 1 hour. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[n] A plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria.

Appendix 2
National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease

NIA/AA Category	Description
Probable dementia: core clinical criteria Meets criteria for dementia described earlier in the text, and, in addition, has the following characteristics:	A. Insidious onset: Symptoms have a gradual onset over months to years, not sudden over hours or days B. Clear-cut history of worsening of cognition by report or observation; and C. The initial and most prominent cognitive deficits are evident on history and examination in one of the following categories: 1. Amnestic presentation: It is the most common syndromic presentation of AD dementia. The deficits should include impairment in learning and recall of recently learned information. There should also be evidence of cognitive dysfunction in at least one other cognitive domain, as defined earlier in the text. 2. Non-amnestic presentations • Language presentation: The most prominent deficits are in word finding, but deficits in other cognitive domains should be present. • Visuospatial presentation: The most prominent deficits are in spatial cognition, including object agnosia, impaired face recognition, simultanagnosia, and alexia. Deficits in other cognitive domains should be present. • Executive dysfunction: The most prominent deficits are impaired reasoning, judgment, and problem solving. Deficits in other cognitive domains should be present. D. The diagnosis of probable AD dementia should not be applied when there is evidence of (a) substantial concomitant cerebrovascular disease, defined by a history of a stroke temporally related to the onset or worsening of cognitive impairment; or the presence of multiple or extensive infarcts or severe white matter hyperintensity burden; or (b) core features of dementia with Lewy bodies other than dementia itself; or (c) prominent features of behavioral variant frontotemporal dementia; or (d) prominent features of semantic variant primary progressive aphasia or non-fluent/agrammatic variant primary progressive aphasia; or (e) evidence for another concurrent, active neurological disease, or a non-neurological medical comorbidity or use of medication that could have a substantial effect on cognition.

Appendix 2: National Institute on Aging/Alzheimer's Association Criteria for Mild Alzheimer's Disease (cont.)

NIA/AA Category	Description
Probable AD dementia with increased level of certainty	**Probable AD dementia with documented decline** In persons who meet the core clinical criteria for probable AD dementia, documented cognitive decline increases the certainty that the condition represents an active, evolving pathologic process, but it does not specifically increase the certainty that the process is that of AD pathophysiology. Probable AD dementia with documented decline is defined as follows: evidence of progressive cognitive decline on subsequent evaluations based on information from informants and cognitive testing in the context of either formal neuropsychological evaluation or standardized mental status examinations. **Probable AD dementia in a carrier of a causative AD genetic mutation** In persons who meet the core clinical criteria for probable AD dementia, evidence of a causative genetic mutation (in APP, PSEN1, or PSEN2) increases the certainty that the condition is caused by AD pathology. The working group noted that carriage of the ε4 allele of the *APOE* gene was not sufficiently specific to be considered in this category.
Probable AD dementia with evidence of the AD pathophysiological process	AD dementia is part of a continuum of clinical and biological phenomena. AD dementia is fundamentally a clinical diagnosis. To make a diagnosis of AD dementia with biomarker support, the core clinical diagnosis of AD dementia must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; *APOE* = apolipoprotein E; CSF = cerebral spinal fluid; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCE

McKhann GM, Knopman DS, Chertkow H, et al. The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:263–9.

Appendix 3
National Institute on Aging/Alzheimer's Association Criteria for Prodromal Alzheimer's Disease (Mild Cognitive Impairment due to Alzheimer's Disease)

NIA/AA Category	Clinical and Cognitive Criteria
Clinical criteria	• Cognitive concern reflecting a change in cognition reported by patient or informant or clinician (i.e., historical or observed evidence of decline over time) • Objective evidence of impairment in one or more cognitive domains, typically including memory (i.e., formal or bedside testing to establish level of cognitive function in multiple domains) • Preservation of independence in functional abilities • Not demented
Etiology of MCI consistent with AD pathophysiological process	• Rule out vascular, traumatic, medical causes of cognitive decline, when possible • Provide evidence of longitudinal decline in cognition, when feasible • Report history consistent with AD genetic factors, when relevant
Prodromal AD dementia with evidence of the AD pathophysiological process	Prodromal AD is part of a continuum of clinical and biological phenomena. Prodromal AD is fundamentally a clinical diagnosis. To make a diagnosis of prodromal AD with biomarker support, the core clinical diagnosis of prodromal AD must first be satisfied. Relevant biomarkers include amyloid-β (CSF or PET) and tau (CSF or PET).

AD = Alzheimer's disease; CSF = cerebral spinal fluid; MCI = mild cognitive impairment; NIA/AA = National Institute on Aging/Alzheimer's Association; PET = positron emission tomography.

REFERENCES

Albert MS, DeKosky ST, Dickson B, et al. The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011;7:270–9.

Appendix 4
Population PK-PET Response Analysis of Gantenerumab Phase III Study WN25203 Data and Aducanumab Phase Ib Study PRIME Data

The population pharmacokinetic positron emission tomography (PK-PET) response analysis of the gantenerumab Phase III Study WN25203 data and aducanumab Phase Ib PET study model was built using pooled information from the gantenerumab Phase III study WN25203 and the aducanumab Phase Ib PRIME study. Details about how this population analysis was conducted and evaluated are provided herein.

1. MATERIALS AND METHODS

1.1 MODELING HYPOTHESIS

Based on the high degree of similarity between gantenerumab and aducanumab, it was assumed that both compounds share the same PK properties in terms of disposition, metabolism, elimination, and the same relationship between in serum concentrations and reduction in standardized uptake value ratio (SUVr) amyloid PET.

It was also assumed that the SUVr data from aducanumab and gantenerumab could be pooled given that they were derived 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.

1.2 PHARMACOKINETIC AND PHARMCODYNAMIC DATA

A PK-pharmacodynamic (PD) dataset for PET model was built using information from the Phase III gantenerumab study (WN25203) together with information from Phase Ib aducanumab trial (PRIME).

2.2.1 Gantenerumab PK and PET Data

2.2.1.1 PK Information

Each patient participating in Study WN25203 provided samples for measurement of their PK serum concentrations at the following scheduled timepoints: Weeks 1, 8, 20, 44, 53, 68, 100, and 101.

The PK data from Study WN25203 were analysed using a population PK model that was previously developed on the basis of Phase I studies.

The Phase I PK database comprised data from 235 patients and healthy volunteers for a total of 4082 PK observations. It contained data from both IV and SC administration, single and multiple repeated doses administered every 4 weeks (Q4W), with dose values ranging for the repeated dose administrations from 6 mg 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

once. A two-compartment model with a 0 order followed by first-order absorption best described the Phase I data. Population parameter values are reported in Table 1.

Table 1 Population PK Parameters Estimated from Phase I Study Data

Parameter	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; PK = pharmacokinetic; POW = power; PROP_ERR = proportional error; Q = intercompartmental clearance; RSE = relative standard error; SLOP = slope; V2 = central compartment; V3 = peripheral volume 3.

The population PK model was used to perform an empirical Bayesian analysis in non-linear mixed-effects model (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 concentrations over the period of observation.

2.2.1.2 PET Information

Among the 799 patients enrolled in Study WN25203, 114 patients participated in the amyloid PET substudy (using the AV-45 ligand). Scans were performed at baseline, Weeks 20, 60, and 100. For patients entering the 2-year, double-blinded portion of the trial (Part 2), another scan was obtained at Week 156.

PET data up to Week 100 (inclusive) were considered for the PK-PD modeling investigations, and the PET database comprised a total of 348 SUVr observations determined using the whole cerebellum as the reference region.

2.2.2 Aducanumab PK and PET PD 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) in March 2015 in Nice, France.

The aducanumab data were collected in the Phase Ib, randomized, double-blind, placebo-controlled study (PRIME) in patients with prodromal or mild Alzheimer's

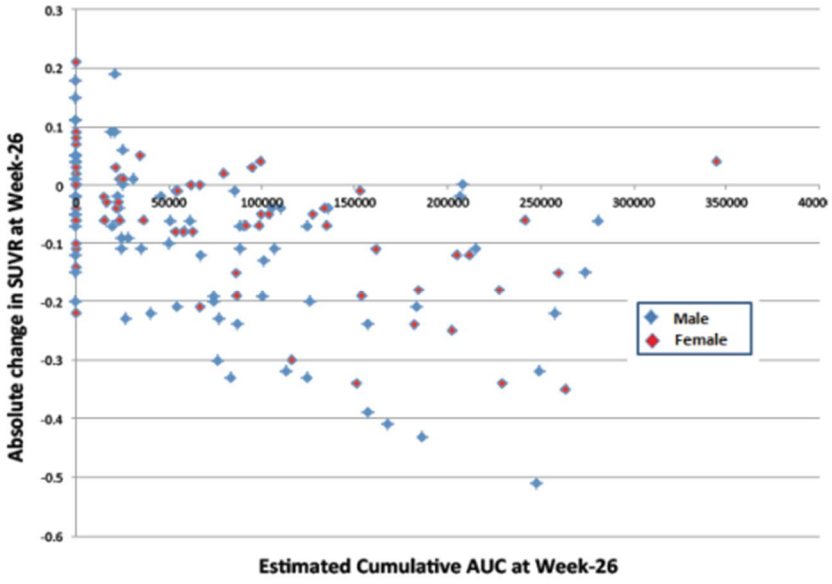
disease. The study design involved a parallel-group design, with a 54-week treatment period. Patients received 14 IV infusions of aducanumab Q4W; four dose groups were evaluated, including the placebo group, and included the 1-mg/kg, 3-mg/kg, 6-mg/kg, and 10-mg/kg dose groups, respectively. SUVr measurements were performed at baseline, Week 26, and Week 54 and were determined using the whole cerebellum as the reference region.

The following figures were used from the aducanumab poster and slides:

- 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 26 (see Figure 1)
- A table presenting the time course of the mean SUVr up to Week 54 by dose group (see Table 2)
- A figure displaying the relationship between the individual cumulative AUC at Week 26 and the four doses investigated in the PRIME study (see Figure 2)

The individual data, as depicted in Figure 1, were extracted and a database of 123 patients with their respective cumulative AUC values at Week 26 and the absolute change from baseline in SUVr. The mean data from Figure 2 were used to extrapolate the individual aducanumab PET data at Weeks 26 to 54 and, also, to assign a mean SUVr baseline value to each aducanumab dose group. In addition, the data from Figure 2 were used to determine from which dose group the individual cumulative AUC values at Week 26 from Figure 1 were most likely derived.

Figure 1 Individual Absolute Change in SUVr Observed in Aducanumab Data at Week 26 with Respect to Cumulative Exposure



AUC = area under the concentration–time curve; SUVr = standardized uptake value ratio.
Source: Hang et al. 2015.

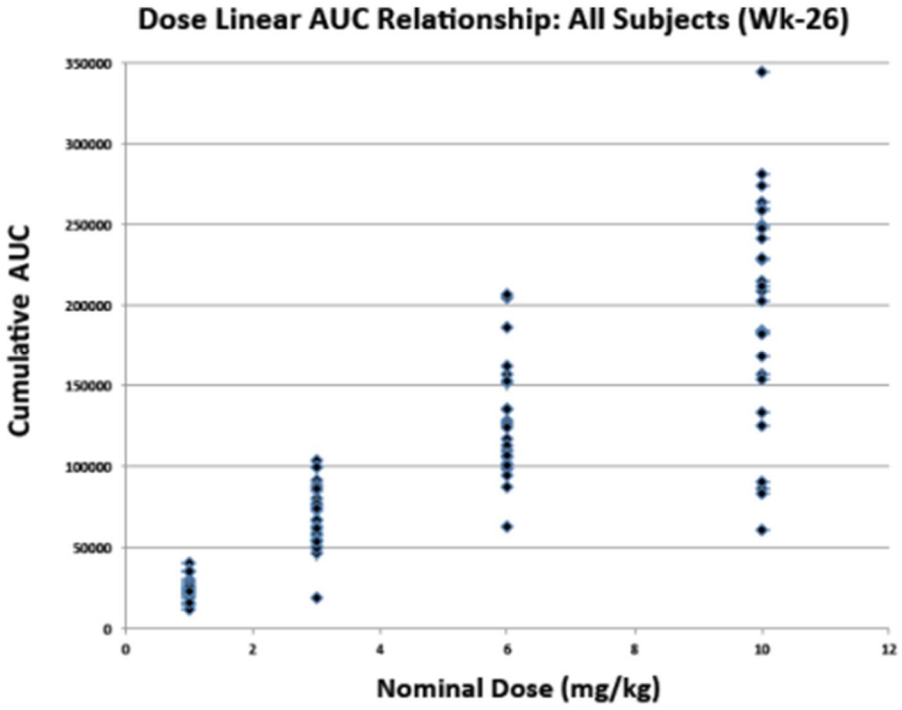
Table 2 Mean Composite PET SUVr Data Observed in the Aducanumab Phase Ib Trial (PRIME) per Dose Group, Using the Whole Cerebellum as Reference Region

	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

SUVr = standardized uptake value ratio.

Source: Data derived from presented slide at ADPD conference.

Figure 2 Individual Dose–Exposure Relationship Observed in the Aducanumab Phase Ib Trial (PRIME)



AUC = area under the concentration–time curve.

Note: Subjects demonstrating low cumulative aducumab exposures were primarily due to missed doses.

Source: Hang et al. 2015.

2.3 POPULATION PK-PD METHODS

2.3.1 Structural PK-PD 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 E_{max} model, and a sigmoid E_{max} model.

No placebo models were evaluated because no specific placebo response was noticed during 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.

Inter-individual 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 means of 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 of >3.84 in OFV (for one degree of freedom), as the difference in OFV is approximately χ^2 distributed.

Additionally, visual predictive check (VPC) was performed to test the model appropriateness by means of computing confidence intervals (CIs) 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 Programs

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 an exploratory graphical analysis of individual post-hoc parameters was conducted only for the following covariates: PET baseline values, compound type, sex, and dose.

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:

$$\mathrm{PET}(\mathrm{time}) = \mathrm{Base} * \left(1 - \mathrm{SLOP} * (\mathrm{Conc_E}(\mathrm{time}))^{\mathrm{POW}}\right)$$

with $$\frac{\mathrm{dConc_E}(\mathrm{time})}{\mathrm{dtime}} = \mathrm{Ke0} * (\mathrm{Conc}(\mathrm{time}) - \mathrm{Conc_E}(\mathrm{time}))$$

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 3.

Table 3 Estimated Population PK-PD Parameters

Parameter	Mean (RSE%)	Value Inter-Individual Variability (RSE%)
Ke0 (Day $^{-1}$)	1.74×10^{-3} (38%)	127.3% (14%)
Equilibration half-life (weeks)	57	
SLOP	0.019 (33%)	—
POW (–)	0.716 (11%)	—
ADD_ERR	0.0659 (5%)	

ADD_ERR = additional error; KeO = rate constant for drug transfer from serum to the effect compartment; PD = pharmacodynamic; PK = pharmacokinetic; POW = power; RSE = relative standard error; SLOP = slope.

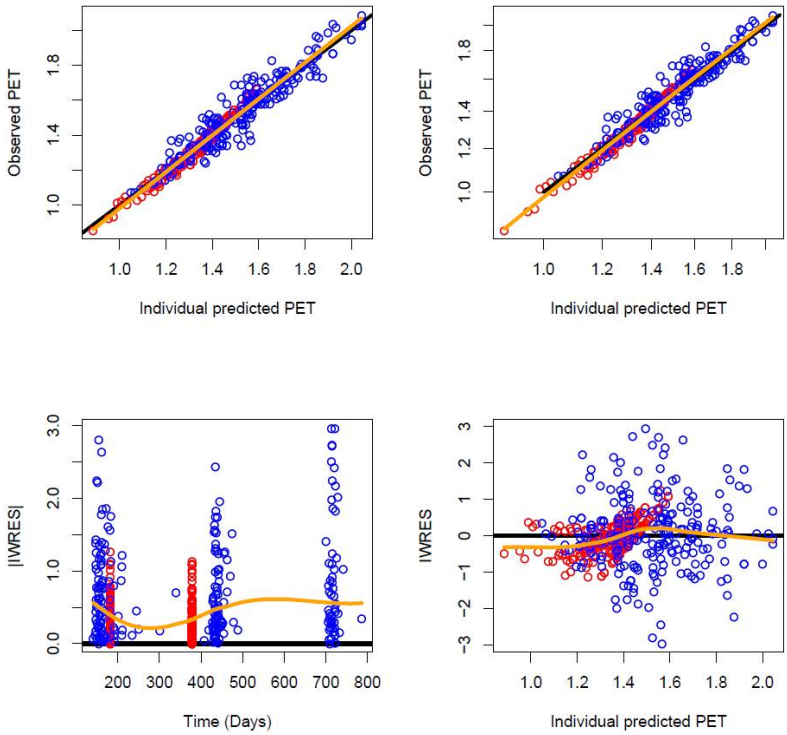
Inspection of the goodness-of-fit plots reported in Figure 3 shows that the final PK-PD model describes the data adequately without obvious bias in the population or individual predicted PET values. The VPCs are shown in Figures 5–7. The shaded areas indicate the 90% CIs (i.e., 5th and 95th percentiles) computed from simulations. The median and

the 5th and 95th percentiles of the observed PK profiles are contained in their respective CIs, 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 4. 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.

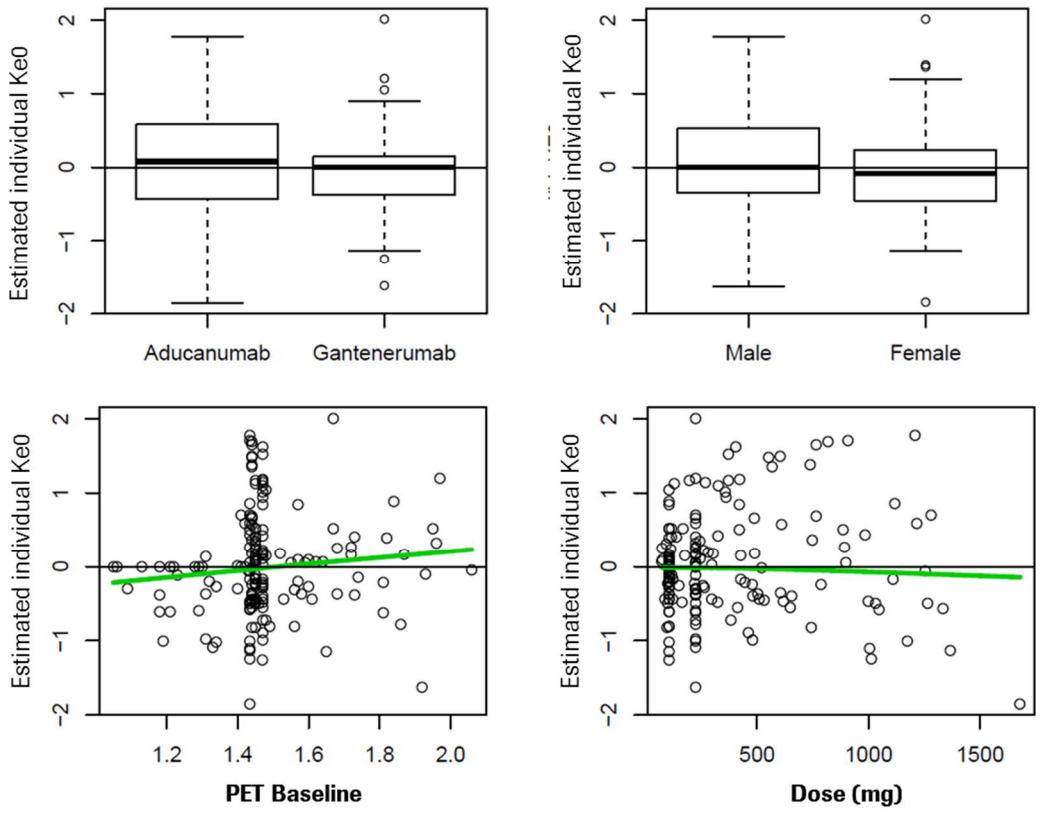
Figure 3 Goodness-of-Fit Plots for the Final PK-PD Model



IWES = individual weighted residual value; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Note: The red dots represent the aducanumab compound, and blue dots represent gantenerumab compound. The orange lines correspond to a smoothing of the data.

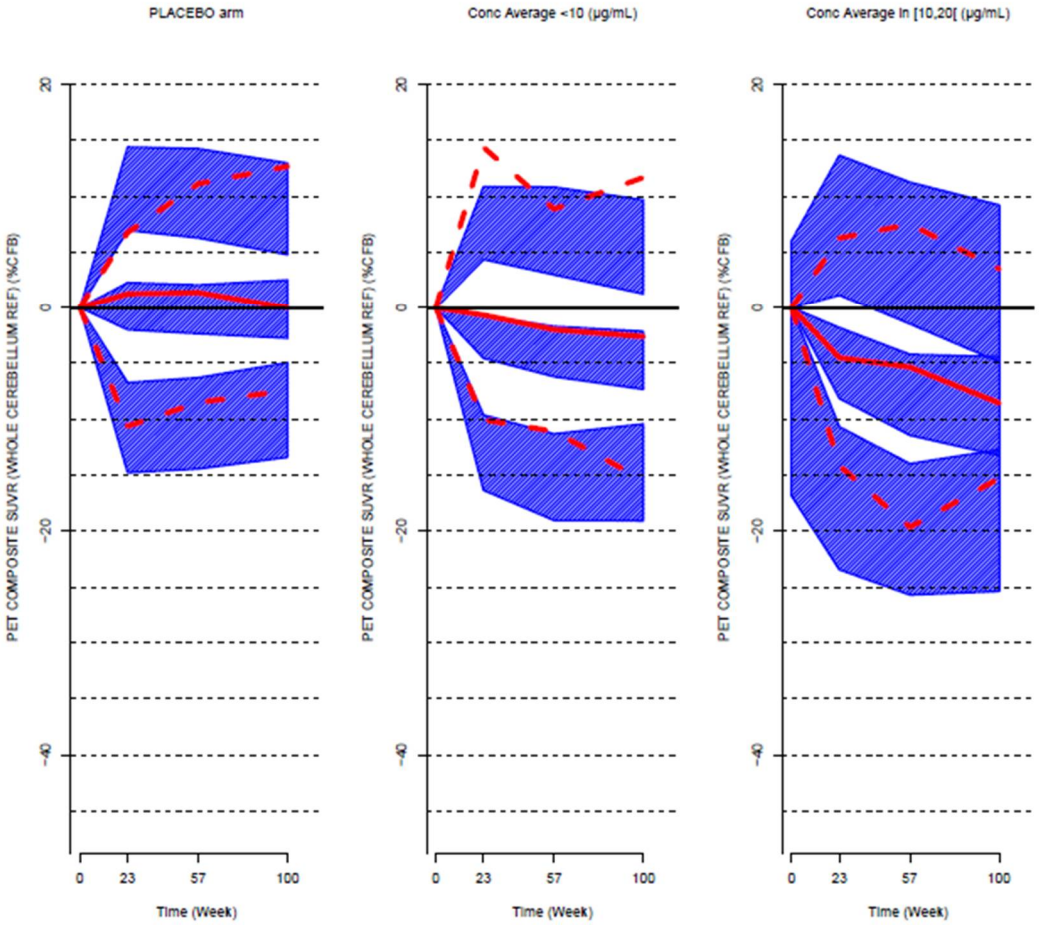
Figure 4 Exploratory Analysis of Covariates (by Compound Type, Sex, PET Baseline Value, and Dose [in milligrams] Value with Respect to Estimated Individual Ke0)



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

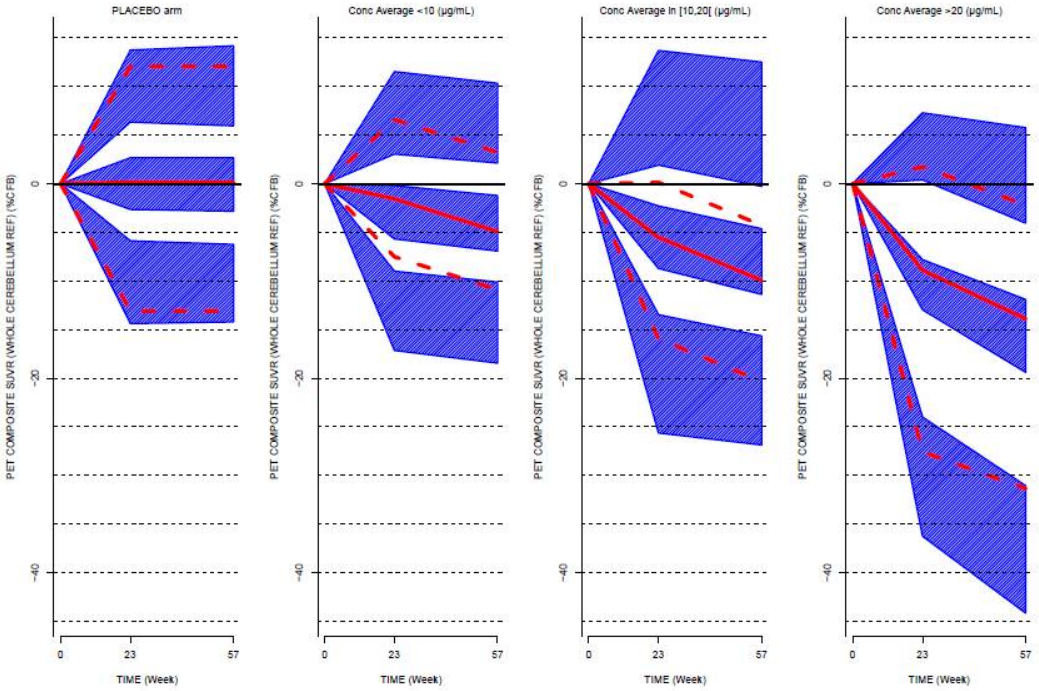
Note: Dose was investigated in milligrams, using a mean weight of 70 kg for doses the aducanumab PRIME study. The green line corresponds to a smoothing of the data.

Figure 5 Visual Predictive Check of the PET Model by Category of Serum Concentration Exposure for the Gantenerumab WN25203 Alone



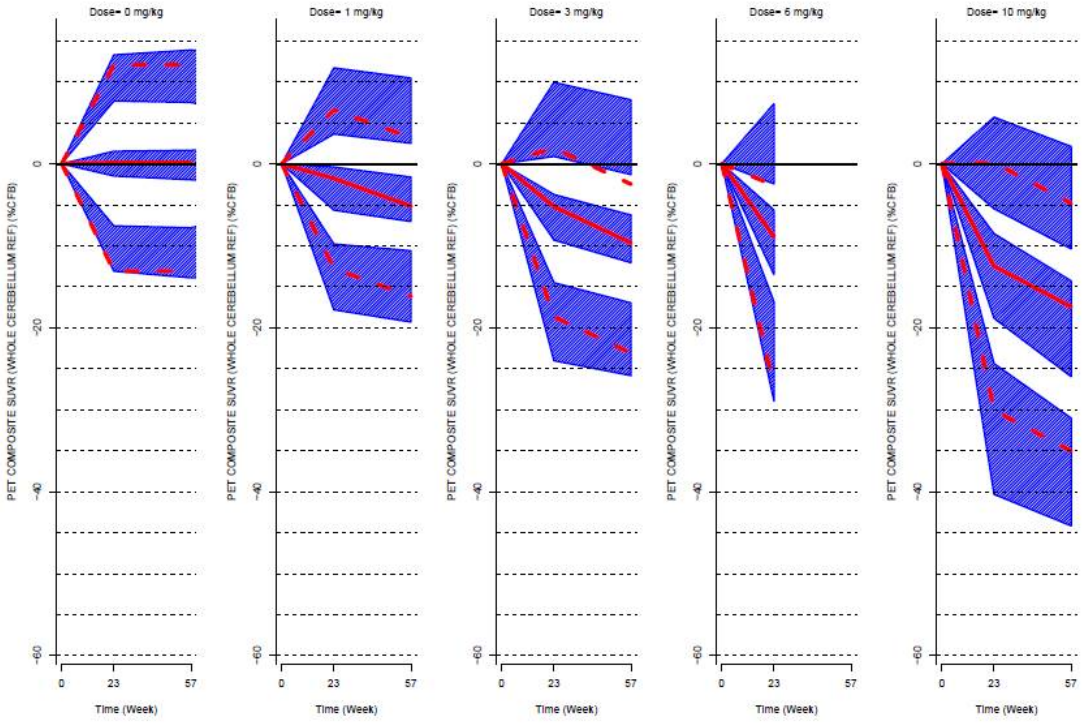
CFB = change from baseline; Conc = concentration; KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 6 Visual Predictive Check of the PET Model Per Category of Serum Concentration Exposure for the Aducanumab PRIME Study Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

Figure 7 Visual Predictive Check of the PET Model by Category of Expected Dose Group for the Aducanumab PRIME Trial Alone



KeO = rate constant for drug transfer from serum to the effect compartment; PET = positron emission tomography; PD = pharmacodynamic; PK = pharmacokinetic.

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Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model

1. BACKGROUND

Hutmacher et al. (2013) presented a pharmacodynamic (PD) model for bapineuzumab addressing the first occurrence of amyloid-related imaging abnormalities, or ARIAs, of "vasogenic edema" (ARIA-E) events. Patients received constant dose regimens of 0.5, 1, and 2 mg/kg given every 13 weeks over 1.5 years. A total of 2435 patients with 243 ARIA-E events were analysed. As shown below, a log hazard model was developed that included three elements:

- A baseline value (I_{BS}) reflecting a constant ARIA-E hazard for apolipoprotein E allele ε4 (*APOE* ε4) gene carriers and non-carriers, respectively.
- Plasma drug concentrations (c) of bapineuzumab modulating the ARIA-E hazard through the maximum effect (E_{max}) of drug and 50% of the effective concentration (EC_{50}) parameters.
- A time component continuously suppressing the ARIA-E hazard by the time (t) since first dosing. ET_{50} and γ modulated this effect.

$$\log h(t) = I_{BS} + \frac{E_{\max} \cdot c(t)}{c(t) + EC_{50}} \cdot \frac{ET_{50}^{\gamma}}{ET_{50}^{\gamma} + t^{\gamma}}$$

Because no model parameters were reported in Hutmacher et al. 2013, the parameters were derived from predicted time-concentration and time-hazard curves presented in Hutmacher et al. 2013 after digitizing the respective graphs for 0.5 mg/kg in *APOE ε4* carriers. I_{BS} parameters were obtained from the graphs directly, whereas the other parameters were calculated from the digitized data using MATLAB (or matrix laboratory) and maximum likelihood estimation. Parameter values are shown in Table 1.

Table 1 Estimated Pharmacodynamic Parameters for Bapineuzumab

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) 3.55E-5 (carrier)	323.441	2.146	6.891	2.64

2. ARIA EVENTS UNDER CONSTANT DOSING REGIMENS

The above model was applied to the double-blind phase of Study WN25203, in which patients received constant dose regimens of 105 and 225 mg of gantenerumab. Owing to paucity of ARIA event data and the assumed independence between time and study drug–related hazard model parameters, I_{BS}, ET_{50}, and γ were fixed to the bapineuzumab values, and only E_{max} and EC_{50} were estimated.

The concentration-time course for gantenerumab in Study WN25203 was derived from a population PK model previously developed for Phase I studies. It covers both intravenous (IV) and subcutaneous (SC) administration, as well as single and multiple repeated doses every 4 weeks, with a range of dose values for the repeated dose administrations from 6 mg to 200 mg for IV administration, 105 mg and 225 mg for SC administration, and up to 300 mg SC and 400 mg for IV administration when given only once. The parameters for this model are presented in Table 2.

Table 2 Pharmacokinetic Parameters for Gantenerumab

CL (L/day)	Q (L/day)	V_2 (L)	V_3 (L)	k_a (1/d)	F1 (1/d)	D (1/d)
0.336	0.869	3.152	6.38	0.22	0.494	0.0821

An update of the population PK model parameters was not considered as newly available drug concentrations were within prediction ranges from the established PK model. The maximum likelihood estimation of the log hazard model parameters E_{max} and EC_{50} was performed using NONMEM software. ARIA-E events were interval censored with a cutoff at 742 days. A total of 797 patients with 50 ARIA-E events were analysed.

Parameter estimates are shown in Table 3.

Table 3 ARIA-E Parameters for Gantenerumab

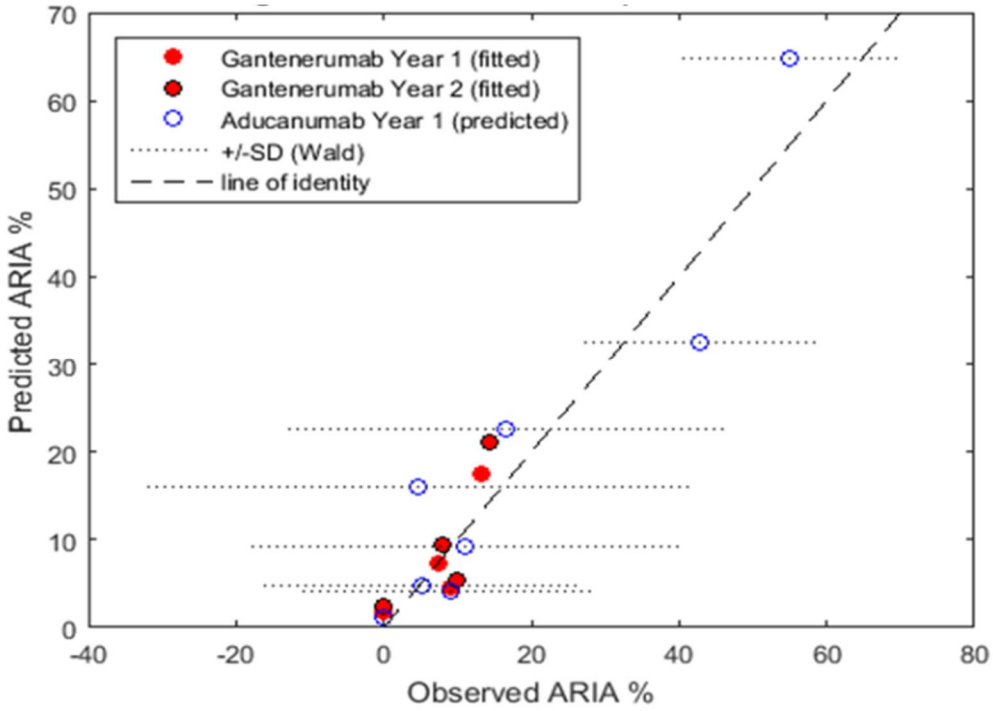
I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
8.7E-6 (non-carrier) F 3.55E-5 (carrier) F	323.44 F	2.15 F	6.05±2.33	8.60±7.13

amyloid-related imaging abnormality–edema/effusion; F = fixed.

On inspection of the aducanumab PRIME study data (Sevigny et al. 2015), it became clear that the PK properties of gantenerumab and aducanumab are very similar. This supported an opportunity to test the hazard PK-PD model applied to gantenerumab on IV aducanumab ARIA-E data. The ARIA-E model, which already provides a good description of the gantenerumab ARIA-E data in Study WN25203 after 1 and 2 years of treatment, respectively, also predicted the aducanumab Phase Ib ARIA-E data with a great degree of accuracy (see Figure 1), including the ARIA rate differences across *APOE* ε4 allele groups (see Figure 2), even though this approach is limited based on external aggregated data. This finding indicated that doses much larger than those

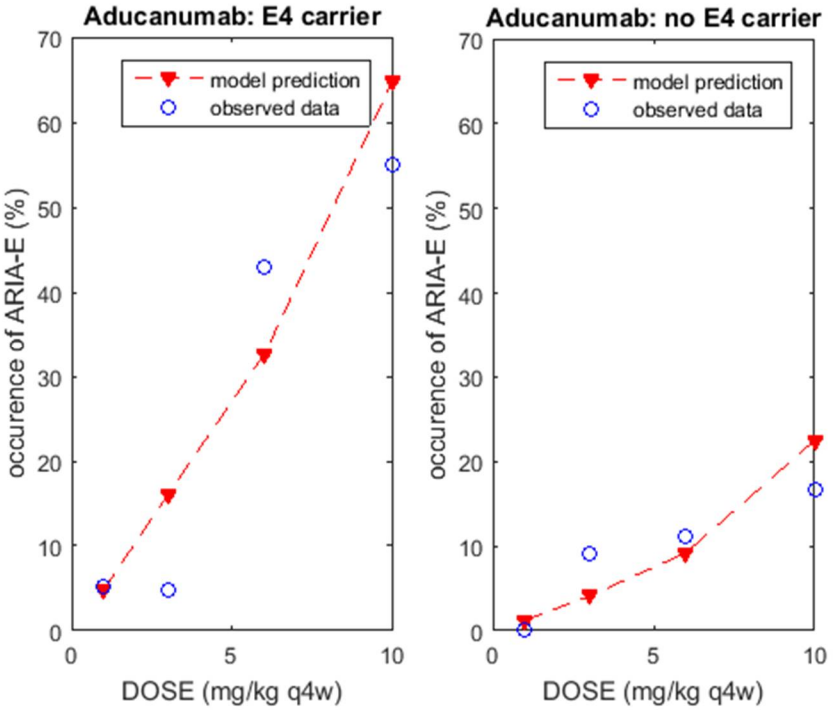
given in Study WN25203 can be described by the hazard model, provided that a constant dose regimen is used.

Figure 1 ARIA-E Prediction for IV Aducanumab Using Bapineuzumab Hazard Model Adapted to SC Gantenerumab



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

Figure 2 Model-Based Predictions of ARIA-E Occurrence for Aducanumab by *APOE ε4* Carrier and Non-Carrier Status and Dose for a Q4W Dosing Regimen: Comparison to Observed Data in the PRIME Study



APOE ε4= apolipoprotein E, allele ε4; ARIA = amyloid-related imaging abnormality; ARIA-E = amyloid-related imaging abnormality–edema/effusion; IV = intravenous; Q4W = every 4 weeks; SC = subcutaneous.

3. ARIA EVENTS UNDER DOSE TITRATION REGIMENS

3.1 MODELING DATABASE AS OF 6 DECEMBER 2016

To check the validity of the model under titration conditions, two patient groups were selected from the open-label extension studies of WN25203 and WN28745. The first group comprised 71 patients who received increasing doses of gantenerumab and received placebo during the double-blind phase of the study. The second group comprised 417 patients who received a constant dose of gantenerumab and who did not have treatment-free intervals of more than 70 days. The first group is representative for the intended Phase III design, and the second group was included to enhance the database and link the model to previously established results (see Table 4).

Appendix 5
Amyloid-Related Imaging Abnormality Hazard Model (cont.)

Table 4 Patient Population Included in ARIA-E Model Building (Database as of 6 December 2016)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (63)**	**371 (35)**	**1168 (108)**	
Placebo treatment	236 (2)	111 (3)	347 (5)	Excluded from model building
Total included in study on active drug	**561 (61)**	**260 (32)**	**821 (103)**	
Total on active drug before OLE, or treatment gaps >70 days	125 (11)	108 (23)	333 (44)	Excluded from model building
Total included in model building	**436 (50)**	**52 (9)**	**488 (59)**	
Titrated without prior treatment	19 (1)	52 (9)	71 (10)	Included in model building
Constant dosing, and treatment gaps <70 days	417 (49)	—	417 (49)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.

As noted previously, the maximum likelihood estimation was performed using NONMEM software. Estimated model parameters were E_{max} , EC_{50} and the baseline risk for carriers and non-carriers. ARIA-E events were observation interval censored.

Parameter estimates are shown in Table 5.

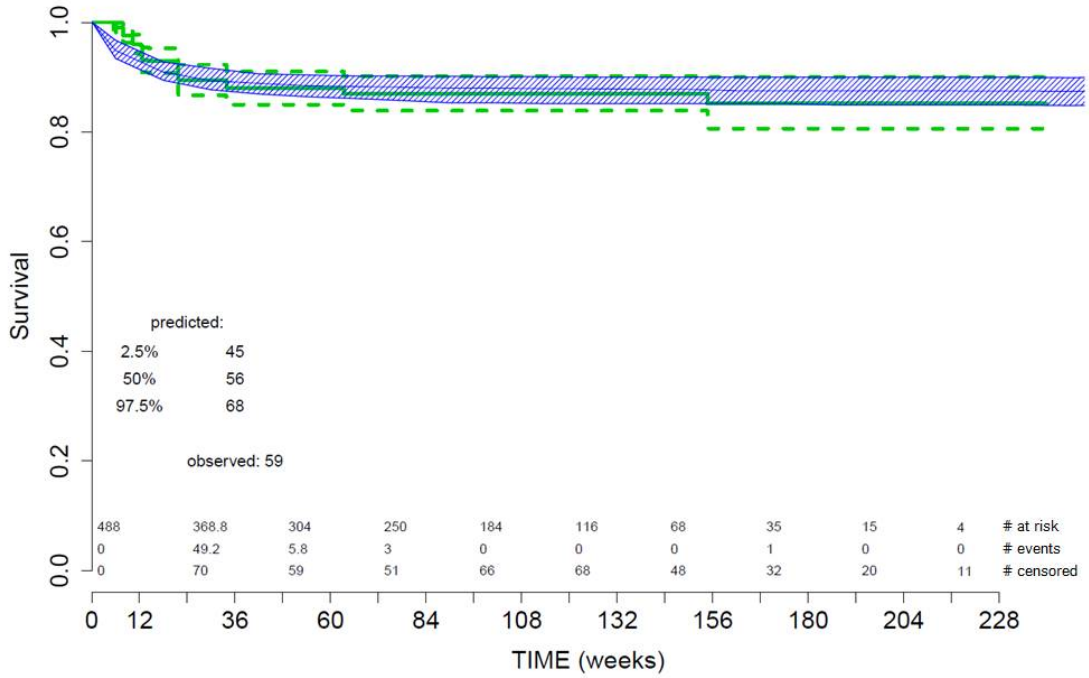
Table 5 ARIA-E Parameters for Gantenerumab When Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
5.84 ± 4.22 E-6 (non-carrier) 11.9 ± 7.30 E-6 (carrier)	323.44 F	2.15 F	7.12 ± 1.03	5.16 ± 2.85

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Visual predictive checks were performed to assess model performance. As shown in Figure 3, the overall model performance was acceptable. Figure 4 presents a condition that was excluded from the model building. The apparent bias in the prediction might be attributable to a SCarlet RoAD study effect, which will be followed up during ongoing completion of the database.

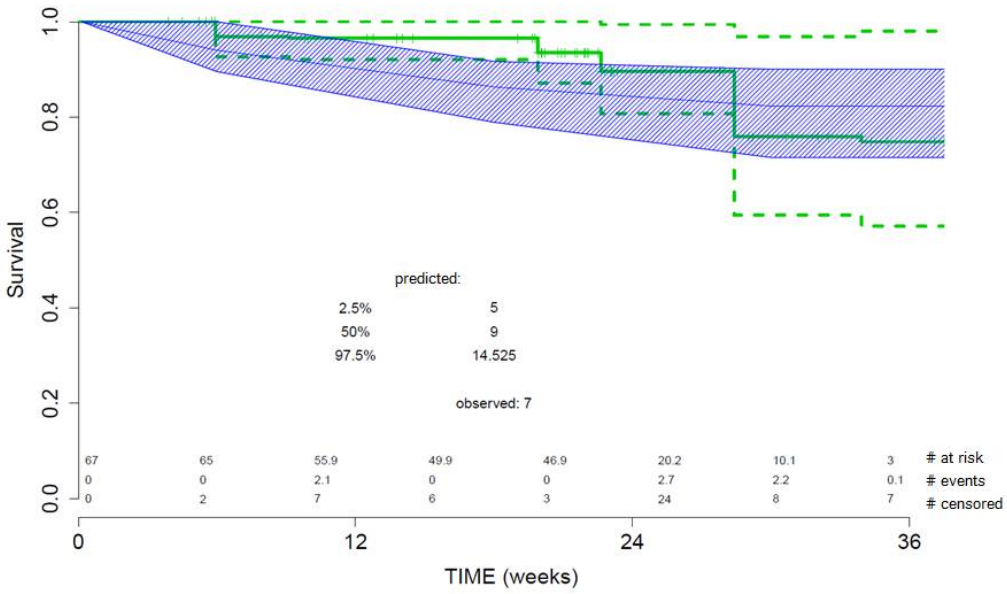
Figure 3 Visual Predictive Check on Database Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

Figure 4 Visual Predictive Checks: Patients in SCarlet RoAD Study with Treatment Interruption >70 Days from Time 0 at Start of Open-Label Extension WN25203



ARIA-E = amyloid-related imaging abnormality–edema/effusion; OLE = open-label extension.
Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% [median], and 97.5%) and the actual observed number of events.

3.2 MODELING DATABASE AS OF 3 MARCH 2017

Table 6 presents an updated ARIA-E model building using data based on the cutoff date of 3 March 2017. In Table 7, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 6 Patient Population Included in ARIA-E Model Building (Database as of 3 March 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	**797 (69)**	**371 (60)**	**1168 (129)**	
Placebo treatment	234 (2)	108 (3)	342 (5)	Excluded from model building
Database cleaning ongoing	3 (0)	—	3 (0)	Excluded from model building
Total included in study on active drug	**560 (67)**	**263 (57)**	**823 (124)**	
Long-term constant dose before titration	64 (9)	83 (17)	147 (26)	Excluded from model building
Total included into model building	**496 (58)**	**180 (40)**	**676 (98)**	
Titrated without prior treatment	24 (2)	67 [18]	91 (20)	Included in model building
Doses always smaller or equal to 225 mg	472 (56)	113 (22)	585 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

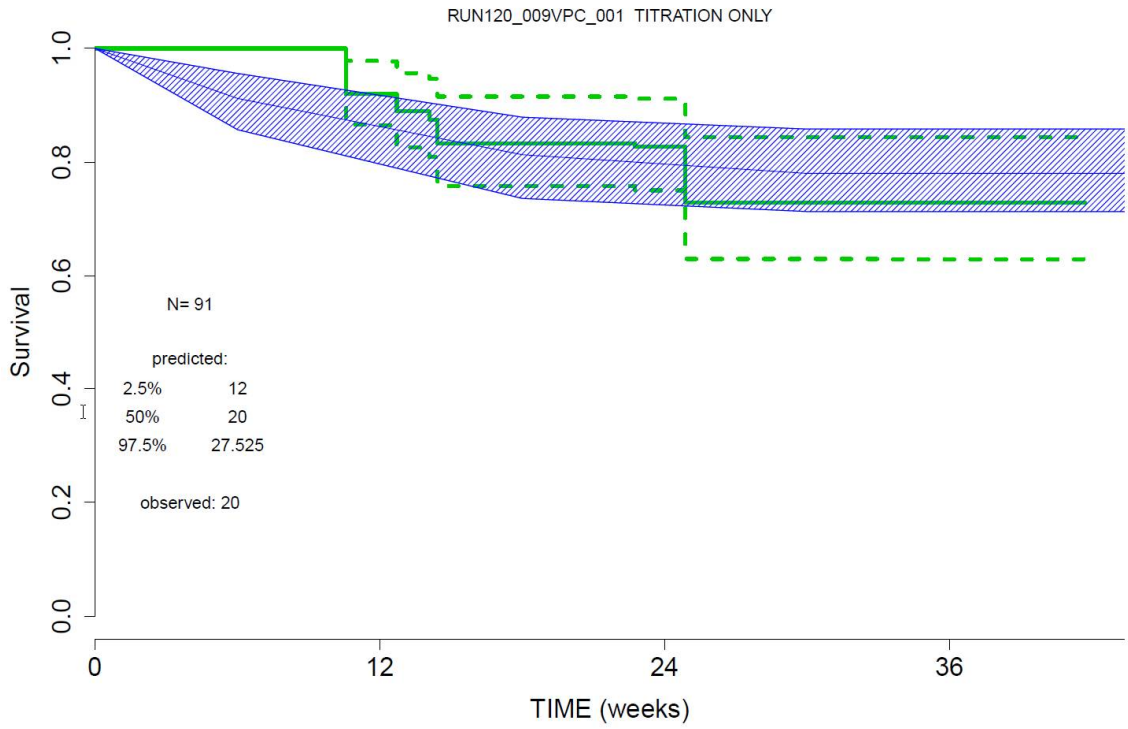
Table 7 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (µg/mL)
2.36 ± 1.01 E-5 (non-carrier) 3.75 ± 1.30 E-5 (carrier)	323.44 F	2.15 F	6.07 ± 0.702	7.75 ± 2.70

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 5–7 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 5 and 6). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

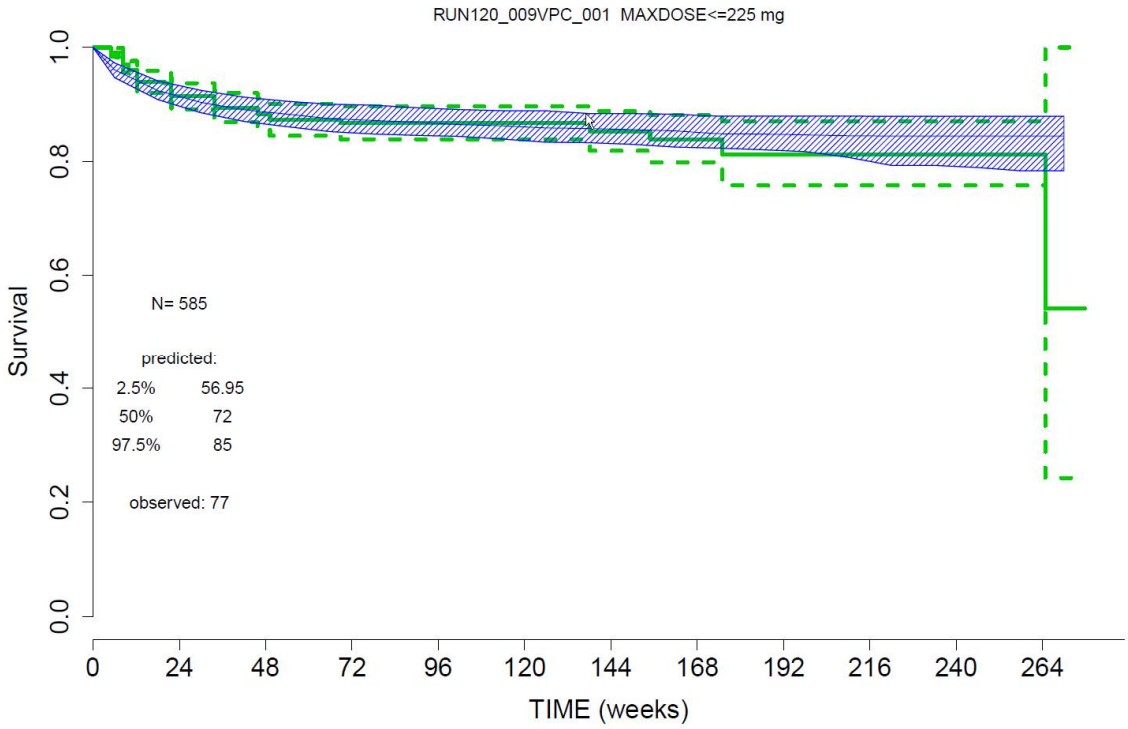
Figure 5 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. The apparent mismatch over the first 12 weeks is because no scan was performed during this period. Survival refers to the ARIA-E event-free proportion.

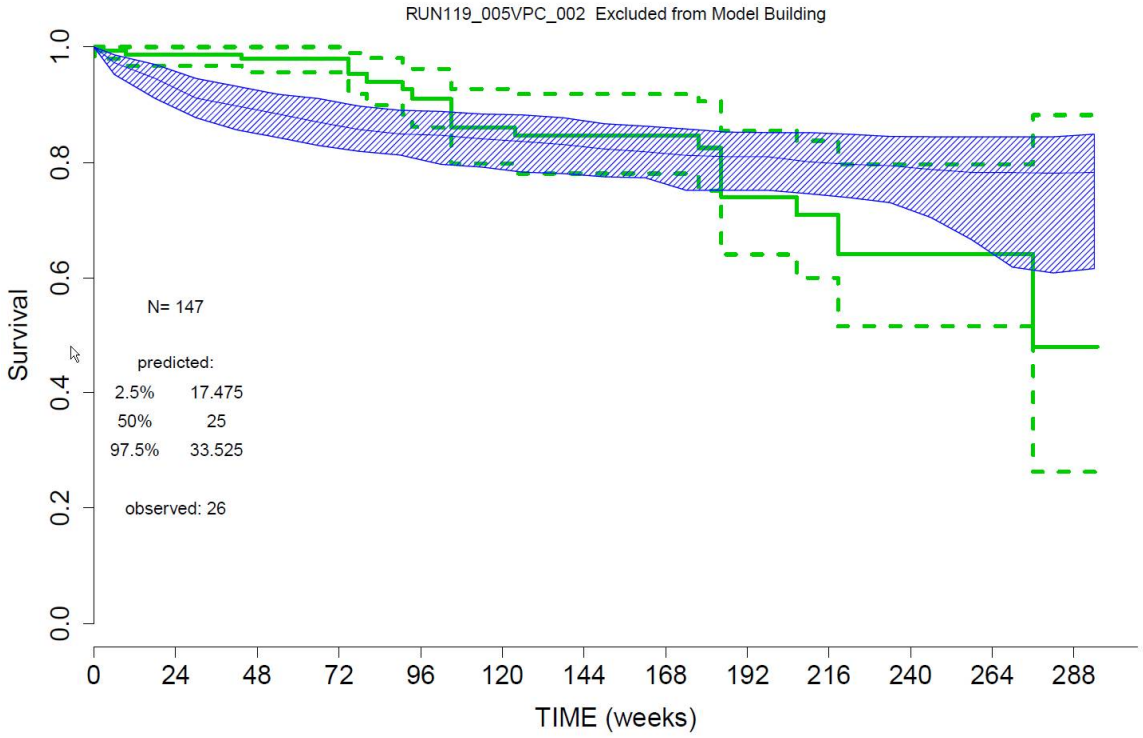
Figure 6 Visual Predictive Check on Data Used for Model Building (Based on Data from Patients Enrolled in the Double-Blind WN25203 and WN28745 Studies and Dosed with 225 mg)



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 7 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

3.3. MODELING DATABASE AS OF 8 JULY 2017

Table 8 presents an updated ARIA-E model building using data based on the cutoff date of 8 July 2017. In Table 9, ARIA-E parameters for gantenerumab are summarized when applied to titration data.

Table 8 Patient Population Included in ARIA-E Model Building (Database as of 7 July 2017)

Number of Patients (Number of Events)	Study WN25203	Study WN28745	Total	Comment
Total included in study	797 (75)	371 (60)	1168 (135)	
Placebo treatment	227 (2)	108 (3)	335 (5)	Excluded from model building
Database cleaning ongoing	2 (0)	—	2 (0)	Excluded from model building
Total included in study on active drug	568 (73)	263 (57)	831 (130)	
Long-term constant dose before titration	66 (14)	80 (16)	146 (30)	Excluded from model building
Total included into model building	502 (59)	183 (41)	685 (100)	
Titrated without prior treatment	36 (3)	70 (19)	106 (22)	Included in model building
Doses always smaller or equal to 225 mg	466 (56)	113 (22)	579 (78)	Included in model building

ARIA-E = amyloid-related imaging abnormality–edema/effusion.

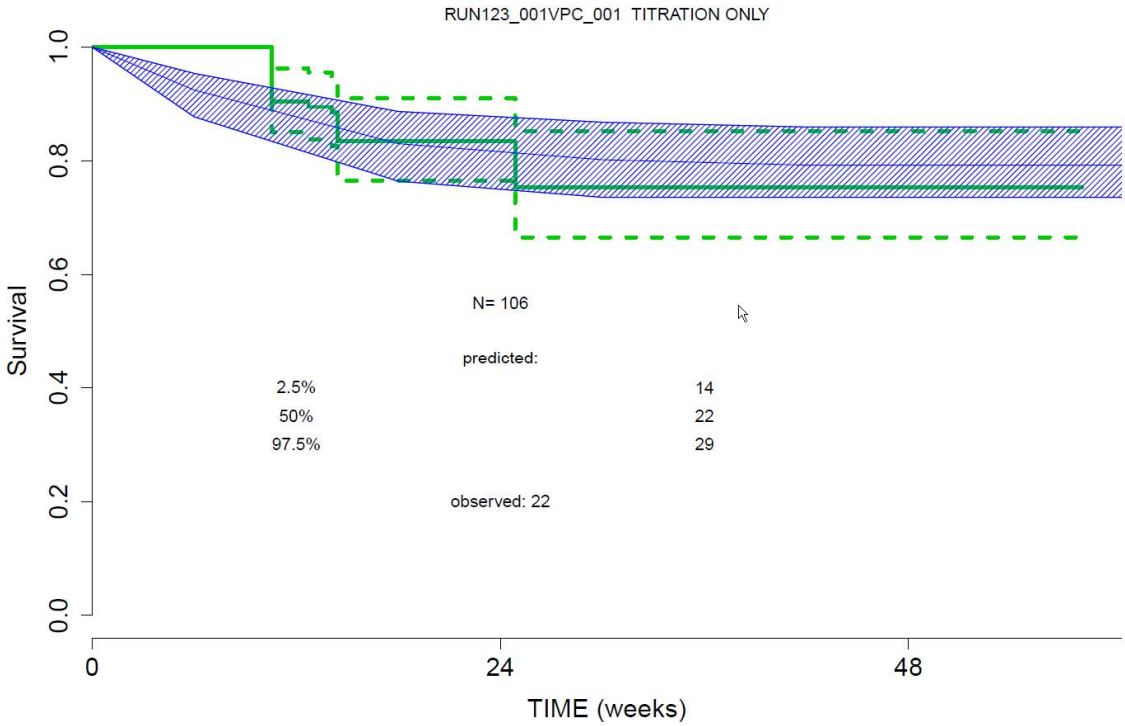
Table 9 ARIA-E Parameters for Gantenerumab when Applied to Titration Data

I_{BS}	ET_{50} (day)	γ	E_{max}	EC_{50} (μg/mL)
2.14 ± 0.9742 E-5 (non-carrier) 3.52 ± 1.24 E-5 (carrier)	323.44 F	2.15 F	5.92 ± 0.688	6.78 ± 2.88

ARIA-E = amyloid-related imaging abnormality–edema/effusion; F = fixed.

Figures 8–10 show visual predictive checks for the final model. For both patients groups selected for model building, the diagnostics look acceptable (see Figures 8 and 9). For the excluded patient group who exhibited constant gantenerumab dosing followed by titration, often with 1 to 2 years of treatment gap in between, the diagnostics indicate a considerable mismatch. This could not be corrected by introducing covariates (such maximum treatment gap) into the model. It appears that the hazard model with its time component is not flexible enough for such regimens.

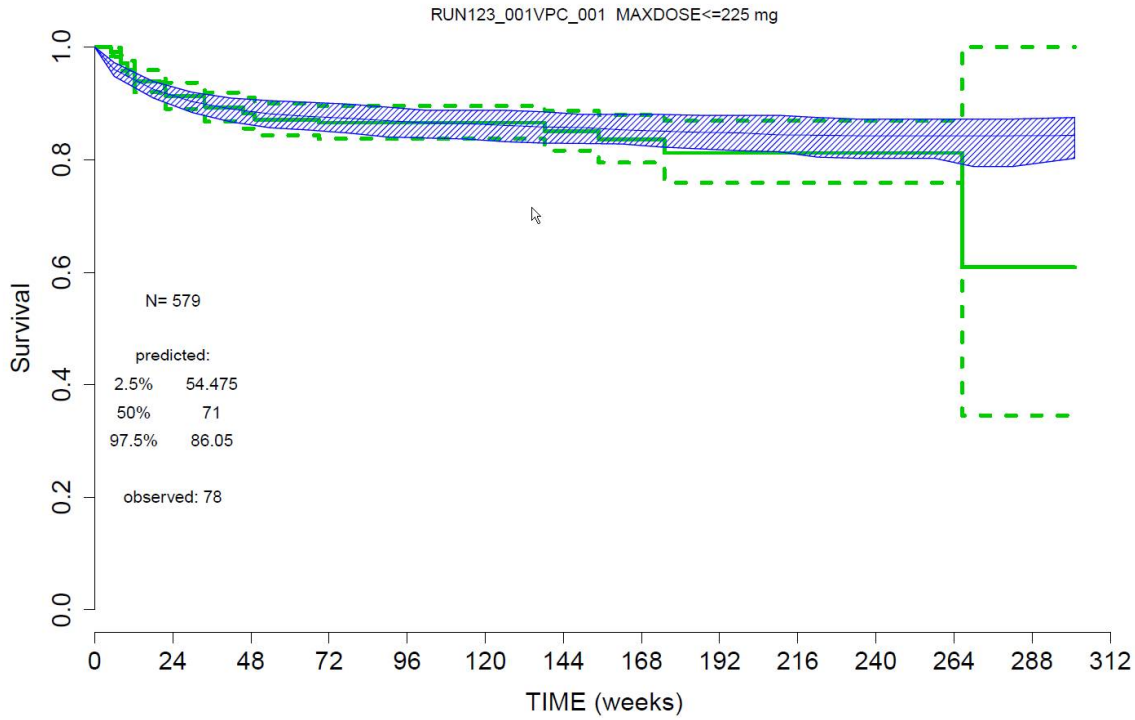
Figure 8 Visual Predictive Check on Titration Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events (2.5%, 50% [median], and 97.5% percentiles), and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

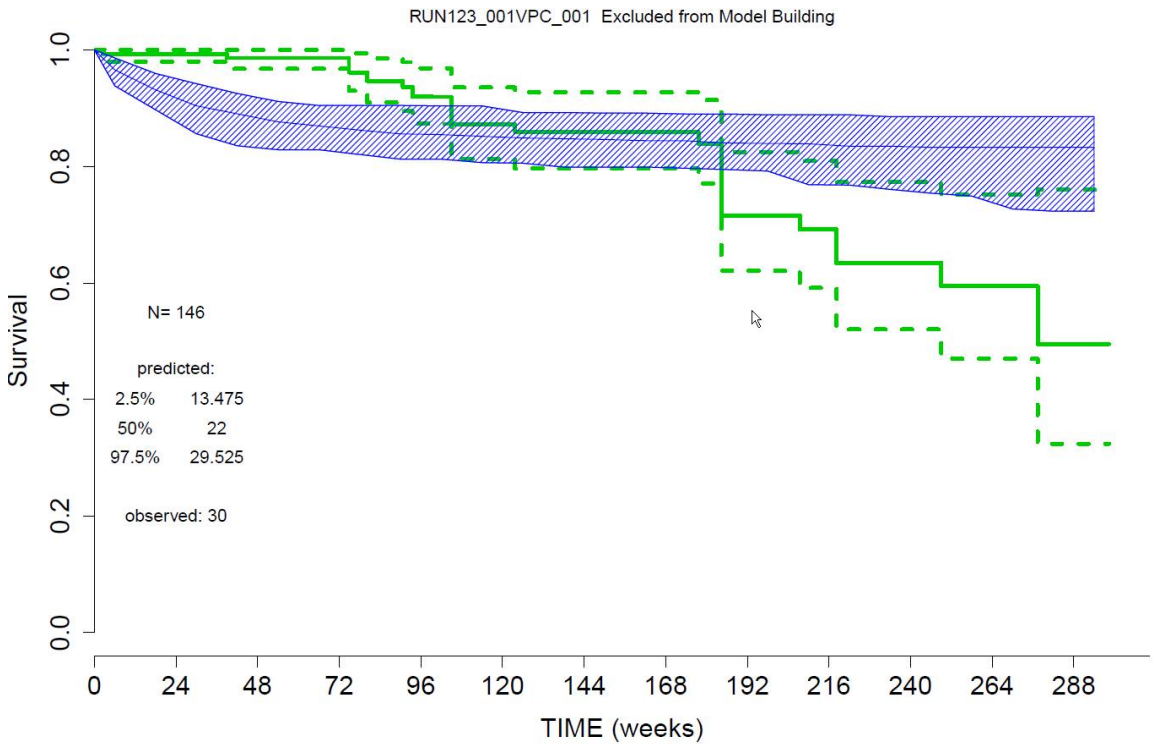
Figure 9 Visual Predictive Check on Data Used for Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

Figure 10 Visual Predictive Check on Excluded Data from Model Building



ARIA-E = amyloid-related imaging abnormality–edema/effusion.

Notes: Kaplan-Meier curves of the data are shown in green (dashed lines: 90% CI). Simulated study data (100 replicated Kaplan-Meier curves) are shown in blue with their mean and 90% CI. Inserted are the number of model-predicted ARIA-E events at given percentiles (2.5%, 50% (median), and 97.5%) and the actual observed number of events. Survival refers to the ARIA-E event-free proportion.

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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.

Appendix 6
Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristics	Action to Be Taken
ARIA-E	Asymptomatic ARIA-E and BGTS <4	• Continue study drug at the same dose level (i.e., do not uptitrate) and repeat MRI scan 4 weeks later. – As long as BGTS is <4 and ≥1, continue study drug at the same dose level and repeat MRI 4 weeks later. – Once ARIA resolves, resume uptitration and obtain an MRI scan per the titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after $ARIA\ resolution$.
	Symptomatic ARIA-E (of any size) or asymptomatic ARIA-E and BGTS ≥4	• Temporarily interrupt study drug and perform MRI scans at 4-week intervals until symptoms and ARIA-E resolve. • When symptoms and ARIA-E resolve, reintroduce study drug at dose given at the time the event was detected. – Perform an MRI scan before next scheduled dose for participants randomized to the Q4W regimen or after the second dose for participant randomized to the Q2W regimen. – If no new ARIA-E is detected, resume uptitration and obtain an MRI per titration schedule. For participants randomized to the Q2W regimen, perform another MRI scan 3 months after study drug reintroduction.
	Any recurrence of ARIA-E	• Treat the same as the first event (based on symptoms and BGTS).
ARIA-H	>15 ARIA-H cumulatively (should not include any disseminated LH)	• Discontinue study drug.

Appendix 6: Management Rules for Amyloid-Related Imaging Abnormalities (cont.)

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H=amyloid-related imaging abnormality–hemosiderin deposition; BGTS=Barkhof grand total score; LH=leptomeningeal hemosiderosis; MRI=magnetic resonance imaging;Q2W=every 2 weeks.

In exceptional cases of (1) an ARIA-E that is asymptomatic with BGTS <4 and considered stable over consecutive MRI images by the Sponsor and investigator; or (2) symptomatic ARIA-E for which the imaging evidence of ARIA-E has resolved but the CNS symptoms continue, study drug can be either reintroduced or uptitrated, as applicable, and 4-weekly MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.

Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are temporally associated with ARIA-E MRI findings

A PK and a plasma biomarker sample will be obtained as soon as is practical (e.g., at an unscheduled visit) once the site becomes aware of the occurrence or worsening of ARIA-E or of the occurrence of ARIA-H meeting discontinuation criteria