Official Title: An Open-Label, Multicenter, Rollover Study to Evaluate the Safety, Tolerability, and Efficacy of Long-Term Gantenerumab Administration in Participants With Alzheimer's Disease

NCT Number: NCT04374253

Document Date: Protocol Amendment 4: 11-May-2022

PROTOCOL

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
PROTOCOL NUMBER:	WN42171
VERSION NUMBER:	4
EUDRACT NUMBER:	2020-000766-42
IND NUMBER:	102,266
NCT NUMBER:	NCT04374253
TEST PRODUCT:	Gantenerumab (RO4909832)
MEDICAL MONITOR:	[redacted], MBBS, Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd
APPROVAL DATE:	See electronic signature and stamp on the final page of this document.

PROTOCOL HISTORY

Protocol		Associated Country-Specific Protocols		
Version	**Date Final**	**Country**	**Version**	**Date Final**
4	See electronic date stamp on the final page of this document.	—	—	—
3 [a]	10 May 2022	—	—	—
2	7 December 2021	China	2	17 December 2021
1	7 March 2020	Taiwan	Addendum 1	15 November 2021
		United Kingdom	Addendum 1	7 April 2021
		France	Addendum 2	7 April 2021
		France	Addendum 1	18 February 2021

[a] Version 3 was demoted incorrectly in anticipation of refinalization, but the final decision is to issue new version to avoid confusion.

PROTOCOL AMENDMENT, VERSION 4:
RATIONALE

Protocol WN42171 has been amended primarily to extend the open-label treatment (OLE) period from 2 to 4 years. The changes to the protocol, along with a rationale for each change, are summarized below. Note that as Version 3 of the protocol was either withdrawn or not submitted, Version 4 will reflect all changes from Version 2 in italics.

- Section 1.3.1 has been updated to reflect that with the 2-year extension participants will receive open-label gantenerumab for up to 4 years.
- Sections 1.2.1 and 1.3.2.3 have been updated to reflect that Studies WN25203 and WN28745 are completed.
- Section 1.3.2.3 has been updated to clarify that no interactions between positron emission tomography (PET) tracers and the coronavirus disease 2019 (COVID-19) vaccines are expected to occur based on the available information.
- The secondary efficacy objective included change over time in cognition and/or function. The reference to “change over time of other outcomes” has been removed since the other outcomes are exploratory efficacy endpoints.
- Section 3.1.1 has been updated to include that the participants will be treated for 4 years with the last visit in the study at OLE-Week 208 and the follow-up visit at OLE-Week 220. The study period extension will allow the collection of more information on the long-term safety and tolerability of gantenerumab in Alzheimer’s Disease (AD) and its efficacy in the context of long-term exposure, thus increasing understanding of gantenerumab’s long term safety and efficacy profile. In addition, it will allow to better understand the long-term effect of gantenerumab on the pathophysiology of AD as well as changes on Study biomarkers.
- Section 3.2 has been updated to reflect that with the 2-year extension, the total duration of the study from baseline visit is expected to be approximately 4 years with the end of the study expected to occur by the end of 2026.
- Section 3.3.3.2 has been added to include the rationale for the additional 2 years. The extension of the study treatment duration from 2 to 4 years will allow the collection of more longitudinal safety and efficacy information of gantenerumab in AD.
- Sections 4.4.1 and 4.4.2 have been updated to reflect less stringent requirements regarding permitted medication that do not have an impact on participant safety and to clarify that study drug should be temporarily interrupted whilst anticoagulation therapy is ongoing.
- Section 4.4.1 has been updated to clarify that the administration of COVID-19 vaccines will be considered, just as with other vaccinations, as a concomitant medication and that it is recommended to avoid vaccination in the 48 hours around the study dug injection to facilitate the correct attribution of adverse events (AEs).

- Section 4.5.3 has been amended to clarify that collecting ethnicity data facilitates evaluation of whether gantenerumab is metabolized or eliminated differently or if the treatment effect will be different in participants of different ethnic origins.
- Sections 4.5.4, 4.5.6.1, 4.5.7.3, 4.5.12, 4.5.13, 4.6.1 and Appendix 1 have been amended to reflect that OLE-W104 is a dosing visit and not the final efficacy and safety visit, to include additional visits during the study extension with the last visit in the study at OLE-Week 208 and to reflect that the follow-up visit will be at OLE-Week 220 and not at OLE-W116.
- Section 4.5.6.13 has been updated to reflect that the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale is also captured electronically. This was omitted in error.
- Section 5.3.5.4 has been amended to clarify reporting of serious or severe secondary events.
- The reporting of adverse events and serious adverse events related to preexisting conditions prior to the parent study baseline has been clarified to ensure the correct collection of data in view of the combined analysis with the data from the parent studies (Sections 5.3.5.12 and 5.3.5.13).
- The Medical Monitor and applicable contact information have been aligned throughout the protocol and deleted from Section 5.4.1. To avoid the inclusion of outdated phone numbers in the protocol, the protocol refers to the Emergency Medical Call Center Help Desk, which will always have an up-to-date list of Medical Monitor and Medical Responsible contact information.

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:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
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MEDICAL MONITOR:	[redacted], MBBS, Ph.D.
SPONSOR:	F. Hoffmann-La Roche Ltd

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

_____
Principal Investigator's Name (print)

_____ _____
Principal Investigator's Signature Date

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

PROTOCOL SYNOPSIS

TITLE:	**AN OPEN-LABEL, MULTICENTER, ROLLOVER STUDY TO EVALUATE THE SAFETY, TOLERABILITY, AND EFFICACY OF LONG-TERM GANTENERUMAB ADMINISTRATION IN PARTICIPANTS WITH ALZHEIMER'S DISEASE**
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IND NUMBER:	102,266
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TEST PRODUCT:	Gantenerumab (RO4909832)
PHASE:	Phase IIIb
INDICATION:	Alzheimer's disease
SPONSOR:	F. Hoffmann-La Roche Ltd

Objectives and Endpoints

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open–label gantenerumab in participants with Alzheimer's disease (AD) who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

Primary Objective: Safety	Corresponding Endpoint
● To evaluate the safety and tolerability of long-term gantenerumab administered by SC injection	● Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events ● Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and C-SSRS ● Nature, frequency, severity, and timing of ARIA-E and ARIA-H ● Nature, frequency, severity, timing, and outcomes of injection-site reactions ● Incidence of treatment discontinuations for adverse events ● Incidence of adverse events of special interest

Secondary Objective: Efficacy	Corresponding Endpoints
● To evaluate the efficacy of long-term gantenerumab administered by SC injection	● The change over time in cognition *and/or* function as measured by the following: – CDR – MMSE – ADAS-Cog11 and ADAS-Cog13 – Verbal Fluency Task – Coding – FAQ – ADCS-ADL
Exploratory Objective: Efficacy	Corresponding Endpoints
● To evaluate the efficacy of long-term gantenerumab administered by SC injection	● The change over time in: – Health-related quality of life, as assessed by the QoL-AD scale – Behavioral and neuropsychiatric symptoms of AD, as measured by the NPI-Q – Caregiver burden, as assessed by the ZCI-AD scale – Elements of resource utilization, as assessed by the RUD-Lite
Exploratory Pharmacokinetic Objective	Corresponding Endpoint
● To characterize the PK profile of gantenerumab administered by SC injection	● Plasma concentration of gantenerumab administered subcutaneously at specified timepoints
Immunogenicity Objective	Corresponding Endpoint
● To evaluate the immune response to gantenerumab administered by SC injection	● Prevalence of ADAs at baseline and incidence of ADAs during the study
Exploratory Biomarker Objective	Corresponding Endpoints
● To evaluate the long-term effects of gantenerumab administered by SC injection	● 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 ● CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, t–tau, and p-tau ● MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter, in all participants. ● Blood and plasma markers over time

Exploratory Health Status Utility Objective	Corresponding Endpoint
• To evaluate the health status utility scores of participants treated with gantenerumab	• Health outcome in participant and caregiver, as measured by EQ-5D

AD=Alzheimer's disease; 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; ARIA-E=amyloid-related imaging abnormality-edema/effusion; ARIA-H=amyloid-related imaging abnormality-microhemorrhage/hemosiderin deposition; CDR=Clinical Dementia Rate; CSF=Cerebrospinal fluid; C-SSRS=Columbia-Suicide Severity Rating Scale; EQ-5D=EuroQoL 5–Dimension Questionnaire; FAQ=Functional Activities Questionnaire; MRI=magnetic resonance imaging; NPI-Q=Neuropsychiatric Inventory Questionnaire; PET=positron emission tomography; PK=pharmacokinetic; p–tau=phosphorylated-tau; SC=subcutaneous; RUD-Lite=Resource Utilization in Dementia–Lite; t-tau=total tau; ZCI-AD=Zarit Caregiver Interview for Alzheimer's Disease.

Study Design

Description of Study

This is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed study WN29922 or WN39658, either the double-blind or open-label extension (OLE) part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow-up, until a day before the first dose in the study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (WN29922 or WN39658) and will be considered the OLE baseline visit (OLE Day 1).
- For participants who completed the double-blind part and the OLE part of study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658. Discussion with the Sponsor is recommended.

Participants with evidence of amyloid-related imaging abnormality–edema/effusion (ARIA-E) on the last per-protocol study magnetic resonance imaging (MRI) scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171.

For those enrolling from the OLE part, the first visit of the participants in study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in the studies WN29922 or WN39658 (e.g., final efficacy and safety visit of the double-blind part, or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study (WN29922 or WN39658) will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. If there is a delay in a participant's transition between the OLE part of the parent study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Sponsor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of the study WN29922 or WN39658, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double–blind part.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for *4* years. *The study duration has been extended from 2 to 4 years in order to collect more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure and to increase the overall number of participant-years of exposure, thus increasing understanding of gantenerumab's long-term safety and efficacy profiles. Unless participants are eligible and choose to enroll in an alternative gantenerumab OLE study that becomes available,* the final dose of study drug will be administered at OLE Week *206*. At the end of the treatment period, all participants will undergo an OLE Week *208* visit. Participants will be asked to come back for a follow-up visit at OLE Week *220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available*.

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log.

Substudies

The substudies associated with study WN42171 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, two optional substudies are associated with Study WN42171: a longitudinal amyloid positron emission tomography (PET) substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable 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 [18F]GTP1 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[18F]GTP1-PET and changes in other endpoints in study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain. The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

Independent Data Monitoring Committee

The independent Data Monitoring Committee (iDMC) will evaluate participant safety 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, amyloid-related imaging abnormality– microhemorrhage/hemosiderin deposition (ARIA-H), and injection site reactions [ISRs]), the iDMC will review all necessary cumulative data, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months *or as detailed in the iDMC charter*. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering 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.

In the event, the iDMC which reviews safety in both the parent studies (WN29922 and WN39658), and study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety *may* be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.

Number of Participants

The planned enrollment is expected to be no more than approximately 2032 participants with AD but will be determined by the number of participants who complete the parent studies WN29922 and WN39658 and enroll in this study.

Target Population

Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg every 2 weeks [Q2W] dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg every 4 weeks [Q4W]), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI)
- The participant should be capable of completing assessments either alone or with the help of the caregiver.
- Availability of a person (referred to as the "caregiver" throughout the protocol) who:
  - In the investigator's judgement, has frequent and sufficient contact (e.g., 5 times per week or approximately 10 hours per week) with the participant;
  - In the investigator's judgement, 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, judgement, 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 caregiver participate throughout the duration of the study.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state ($\geq$12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - 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 adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- 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.

Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication

- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

End of Study

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of *2026*.

In addition, the Sponsor may decide to terminate the study at any time.

Length of Study

The total length of this study from baseline visit (OLE Day 1 in either the Study WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately *4* years and 3 months. Following uptitration, participants will receive up to *86* doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

Investigational Medicinal Products

The investigational medicinal product for this study is gantenerumab.

Test Product (Investigational Drug)

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

Statistical Methods

Primary Analysis

The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

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

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in a Statistical Analysis Plan (SAP).

Determination of Sample Size

The sample size will include all eligible participants who consent to this study. The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete the parent studies (WN29922 and WN39658) and enroll in this study.

Interim Analyses

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analysis(es), which may include efficacy, safety, and biomarker outcomes. An interim analysis may be considered when the parent pivotal studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in a SAP.

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
[^{18}F]GTP1	Genentech Tau Probe 1
Aβ	amyloid beta
AChEI	acetylcholinesterase inhibitor
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	Apolipoprotein E
APOE ε4-	apolipoprotein E gene allele ε4-
ARIA	amyloid-related imaging abnormality
ARIA-E	amyloid-related imaging abnormality–edema/effusion
ARIA-H	amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition
BOLD	blood oxygenation level-dependent
CDR	Clinical Dementia Rating
CDR-GS	Clinical Dementia Rating–Global Score
CDR-SOB	Clinical Dementia Rating–Sum of Boxes
COA	clinical outcome assessment
COVID-19	coronavirus disease 2019
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
DTI	diffuse tensor imaging
DSST	Digit Symbol Substitution Test
EC	Ethics Committee
eCRF	electronic Case Report Form
EDC	electronic data capture
EQ-5D	EuroQoL 5-Dimension Questionnaire
E.U.	European Union
FA	fractional anisotropy
FAQ	Functional Activities Questionnaire
FDA	(U.S.) Food and Drug Administration

Abbreviation	Definition
GRE	gradient recalled echo
GTP1	Genentech Tau Probe 1
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Council for Harmonisation
iDMC	independent Data Monitoring Committee
IMC	Internal Monitoring Committee
IMP	investigational medicinal product
IND	Investigational New Drug (Application)
IRB	Institutional Review Board
ISR	injection-site reaction
IxRS	interactive voice or web-based response system
MAD	multiple ascending dose
MMSE	Mini-Mental State Examination
MN	mobile nursing
MRI	magnetic resonance imaging
MR-NP	Marguerite RoAD (Study WN28745) double-blind placebo (non-pretreated patients in the placebo arm of Study WN28745 during the double-blind phase)
MR-P	Marguerite RoAD (Study WN28745) double-blind active (pretreated patients in the active treatment arm of Study WN28745 during the double-blind phase)
NMDA	N-methyl-D-aspartate
NPI-Q	Neuropsychiatric Inventory Questionnaire
OLE	open-label extension
PD	pharmacodynamics
PET	positron emission tomography
PK	pharmacokinetic
p-tau	phosphorylated tau
Q2W	every 2 weeks
Q4W	every 4 weeks
QoL	quality of life
QoL-AD	Quality of Life–Alzheimer's Disease
RBR	Research Biosample Repository
rs-fMRI	resting-state functional magnetic resonance imaging
RUD-Lite	Resource Utilization in Dementia–Lite
SAP	Statistical Analysis Plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SR	Scarlet RoAD (Study WN25203)
T4	thyroxine

Abbreviation	Definition
t-tau	total tau
ULN	upper limit of normal
WAIS-IV	Wechsler Adult Intelligence Scale-Fourth Edition
WES	whole exome sequencing
WGS	whole genome sequencing
ZCI-AD	Zarit Caregiver Interview for 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 to 152 million by 2050. Alzheimer's disease (AD) is the most common form of dementia, accounting for 60%–70% of cases (World Health Organization 2019). 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.

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; Zanetti et al 2009), but some individuals 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 in the European Union and United States to treat the symptoms of AD, including acetylcholinesterase inhibitors (AChEIs) and N-methyl-D-aspartate (NMDA) 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. 2018).

Currently, one compelling therapeutic target (Graham et al. 2017) is amyloid beta (Aβ), and Aβ-targeting therapies remain the major trend in AD drug development (Bachurin et al. 2017). These therapies are based on the amyloid hypothesis that posits Aβ accumulation as the primary factor driving AD 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.

1.2 BACKGROUND ON GANTENERUMAB

Gantenerumab (RO4909832) is a recombinant, human monoclonal antibody of the IgG1 subclass directed against the Aβ peptide. Gantenerumab recognizes a conformational epitope of Aβ and has demonstrated activity for both major types of Aβ (Aβ1–40, Aβ1–42). In vitro, gantenerumab recognizes synthetic aggregated Aβ fibrils and Aβ oligomers with high nanomolar affinity (K_D, ~0.6–1.2 nM). The mechanism of action of gantenerumab is primarily clearance of Aβ plaques by antibody-dependent cell-mediated

phagocytosis. Gantenerumab also works via dissociation of Aβ peptide aggregates by direct resolution and by blockade of toxic Aβ oligomers.

Gantenerumab is manufactured by cell culture of a recombinant Chinese hamster ovary K1 mammalian cell line and subsequent purification of the antibody. Gantenerumab drug substance manufacturing was optimized during development to improve process robustness and increase overall process yield, leading to several generations of manufacturing process (G1, G2, G3, and G4). Drug material manufactured by the G4 process is used in pivotal Phase III clinical trials (Studies WN29922 and WN39658). G4 drug material will be used in this study.

1.2.1 Nonclinical and Clinical Studies

Nonclinical evidence has suggested that monoclonal anti-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 of 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; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in the cerebrospinal fluid (CSF;Roche Research Report No. 1066251). In a Phase I study with the anti-Aβ monoclonal antibody aducanumab, reduction of deposited amyloid as shown on brain amyloid positron emission tomography (PET) imaging was associated with a time- and dose-related slowing of cognitive decline (Sevigny et al. 2016). Because the pathological 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, such as Aβ oligomers, fibrils, and plaques, is expected to address this need (Bohrmann et al. 2012).

Gantenerumab has been investigated in 10 completed Phase I clinical studies: 3 single ascending dose studies in healthy volunteers and patients with mild to moderate AD (Studies BN18726, JP22474, and BP30042); 2 multiple ascending dose (MAD) studies of patients with mild to moderate AD (Studies NN19866 and JP22431); and 4 bioavailability studies in healthy subjects−1 study comparing the IV and SC formulations of gantenerumab (Study WP22461), 2 studies comparing lyophilized and high-concentration liquid formulations of gantenerumab (Studies WP27951 and BP29113), and 1 study comparing drug substance manufactured through the third and fourth generation (G3 and G4) processes (Study WP40052). A tolerability study that compared injection-site pain between faster and slower SC administration of gantenerumab was also conducted (Study WP39322). Overall, a total of 543 subjects

have participated in the Phase I studies; of these participants, 406 healthy volunteers and 101 patients with mild to moderate AD have received gantenerumab.

Based on results of the MAD Study NN19866 and of the relative bioavailability study (WP27951), the doses of 105 mg SC every 4 weeks (Q4W; equivalent to 60 mg IV Q4W) and 225 mg SC Q4W (equivalent to 130 mg IV Q4W) were initially selected for the Phase III studies WN25203 and WN28745. Following the results of the Study WN25203 futility analysis, these studies were converted into open-label extensions (OLEs) to examine the safety and tolerability of a higher dose of gantenerumab (1200 mg SC Q4W).

Overall, 383 patients enrolled in the OLEs of Studies WN25203 and WN28745. As of 1 May 2019, 363 patients had been exposed to G3 gantenerumab doses higher than 225 mg, and 309 patients reached the target 1200 mg dose. Continuous monitoring of safety data and magnetic resonance imaging (MRI) findings by the Sponsor has not identified any new safety signals in these ongoing studies. Injection-site reactions (ISRs) and amyloid-related imaging abnormalities (ARIAs) remain the only identified risks for gantenerumab. These OLE studies *were completed respectively in 2020 and* in 2021, and patients who *did* not discontinue study treatment at the end of the prescribed study period *were* provided an option to enroll in an open-label rollover study to evaluate the safety and tolerability of long-term administration of gantenerumab (Study WN41874).

Based on safety results from OLE Studies WN25203 and WN28745, and on data from the PET substudies that confirmed the pharmacodynamic (PD) effects of gantenerumab treatment (1200 mg SC Q4W) on Aβ plaque reduction (Klein et al. 2019b), two pivotal multicenter, Phase III studies in patients with early (prodromal to mild) AD were initiated: WN29922 (Graduate 1) and WN39658 (Graduate 2). These studies are examining the efficacy, safety, and tolerability of gantenerumab uptitrated to 510 mg every 2 weeks (Q2W) dosing; they are currently ongoing and are expected to be completed in 2023. Refer to the Gantenerumab Investigator's Brochure for more details on nonclinical and clinical studies.

1.3 STUDY RATIONALE AND BENEFIT–RISK ASSESSMENT

1.3.1 Study Rationale

Study WN42171 allows participants previously treated with gantenerumab or placebo for approximately 2 years in the parent Studies WN22992 or WN39658 to continue receiving open-label gantenerumab.

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 a factor contributing to AD progression (Sun et al. 2015). Thus, the targeting of Aβ and

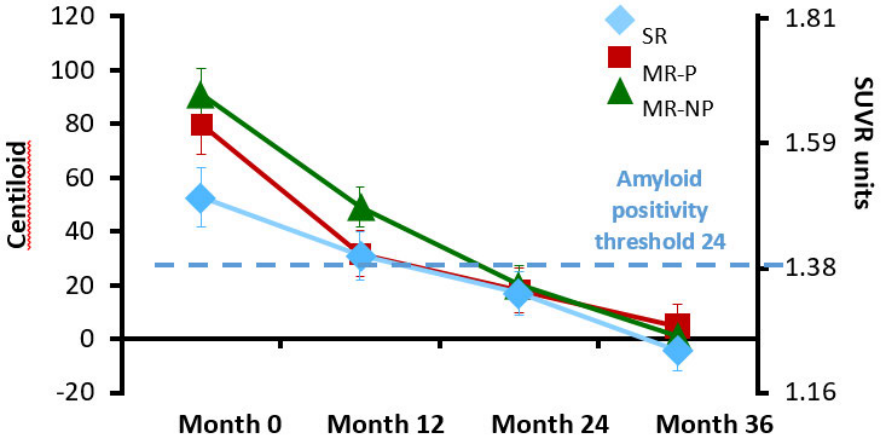
subsequent displacement of Aβ from the brain is a rational approach to modify AD progression.

Accumulating clinical evidence supports that monoclonal Aβ antibodies can bind Aβ and promote its clearance (Salloway et al. 2009; Ostrowitzki et al. 2012; Sevigny et al. 2016; Klein et al. 2019b), reduce deposition of Aβ aggregates, and reduce markers of neurodegeneration in CSF (Ostrowitzki et al. 2017). A Phase I study of aducanumab (Sevigny et al. 2016) and a Phase II study of BAN2401 (Swanson et al. 2018) suggested that reduction of deposited amyloid, as seen on brain amyloid PET imaging, was associated with a dose-related slowing of cognitive decline.

Gantenerumab data from the PET substudies of the WN25203 and WN28745 OLEs confirmed that gantenerumab treatment at a dose of 1200 mg SC Q4W reduced Aβ plaques in patients with AD (Klein et al. 2019b). Overall, 89 patients from the OLEs of Studies WN25203 and WN28745 were included in amyloid PET substudies using florbetapir F18. As of 31 August 2019, of these 89 patients, 67 patients received follow-up scans at Week 52, 42 patients at Week 104, and 30 patients at Week 156 of the OLE.

Results of the PET substudies showed a marked and consistent reduction of amyloid load in patients receiving higher-dose gantenerumab in all three patient groups that were analyzed (Figure 1): 1) MR-NP (non-pretreated patients in the placebo arm of Study WN28745); 2) MR-P (pretreated patients in the active treatment arm of Study WN28745); and 3) SR (patients from Study WN25203). Indeed, amyloid reductions were seen consistently in nearly all patients in the three analyzed subgroups (Figure 2).

Figure 1 Mean (SE) PET Amyloid Reductions in the OLE PET Substudies



Centiloids[a]				
SR	52.7 (11.1) n = 20	30.9 (8.9) n = 19	17.0 (8.2) n = 13	**–4.3 (7.5)** n = 10
MR-P	79.6 (10.9) n = 21	31.7 (8.6) n = 21	18.1 (8.3) n = 11	**4.7 (8.0)** n = 8
MR-NP	91.1 (9.6) n = 27	49.1 (7.6) n = 27	20.2 (7.0) n = 18	**0.78 (6.7)** n = 12

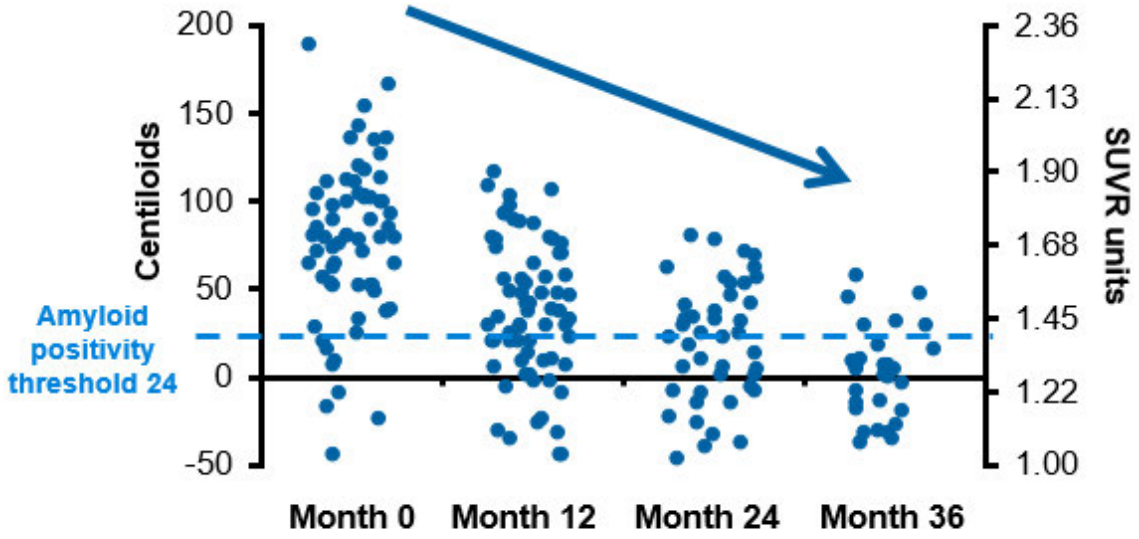
MR-P=Marguerite RoAD (Study WN28745) double-blind active (pretreated patients in the active treatment arm of Study WN28745 during the double-blind phase); MR-NP=Marguerite RoAD (Study WN28745) double-blind placebo (non-pretreated patients in the placebo arm of Study WN28745 during the double-blind phase); OLE = open-label extension; PET = positron emission tomography; SE = standard error; SR = Scarlet RoAD (Study WN25203); SUVR = standardized uptake value ratio.

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

Source: Klein et al. 2019a.

The threshold for amyloid positivity is an important anchor for interpreting the PET substudy results. It is defined as 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 (Landau and Jagust 2015; Navitsky et al. 2018; Klein et al. 2019b). Results in the ongoing substudies WN25203 and WN28745 confirm the amyloid plaque removal component of the gantenerumab mechanism of action. The results further show that following 3 years of gantenerumab treatment, 80% of subjects were below the positivity threshold, and 43% of subjects were below a centiloid value of 0, which represents the mean amyloid load of a healthy normal population (Figure 2).

Figure 2 Patient-Level Amyloid Reductions over 3 Years of Treatment in the OLE PET Substudies



Proportion of participants below amyloid positivity threshold

No. of participants	68	67	42	30
% below threshold	**15%**	**37%**	**52%**	**80%**

OLE = open-label extension; PET = positron emission tomography; SUVR = standardized uptake value ratio.
Source: Klein et al. 2019a.

In summary, the PET substudy results demonstrate continued amyloid removal beyond 2 years of gantenerumab treatment. Thus, this study, which provides open-label gantenerumab for 4 additional years to patients already receiving gantenerumab in the parent Study (WN22992 or WN39658), will provide valuable information on how continued amyloid removal may translate into continued clinical effect.

Study WN42171 will also provide the opportunity for participants previously treated with placebo in the double-blind phase of parent Study WN22992 or WN39658 to receive gantenerumab treatment for up to 4 years. To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, treatment assignment information from the double-blind phase of parent Study WN22992 or WN39658 will remain blinded to the Sponsor, investigator, and participant at least until database lock of the parent studies, which will happen while this study is ongoing.

1.3.2 Safety Overview

Nonclinical characterization of gantenerumab did not show relevant safety findings. No differences between gantenerumab and placebo groups have been observed in laboratory parameters, physical and neurologic examinations, vital signs, or ECG parameters.

The identified risks of gantenerumab treatment are ARIAs and ISRs. Safety data and MRI findings are continuously monitored in all ongoing studies, and no new safety signals have been identified.

The Gantenerumab Investigator's Brochure includes a summary of safety data with gantenerumab SC in participants with AD from Studies WN25203 and WN28745 as well as from Phase I studies with gantenerumab SC and IV.

Providing participants who complete study treatment in the pivotal Studies WN22992 and WN39658 with an opportunity to extend or initiate treatment with open-label gantenerumab in Study WN42171 will allow the collection of more information on the long-term safety and tolerability of gantenerumab in AD. It will also provide more information on its efficacy in the context of long-term exposure. Furthermore, the OLE will increase the overall number of participants exposed to gantenerumab and participant-years of exposure, thus increasing understanding of the safety and efficacy profiles.

1.3.2.1 Amyloid-Related Imaging Abnormalities

ARIAs are one of the most significant adverse events reported in therapies against aggregated forms of Aβ. These findings appear to be dependent on dose-, time-, and apolipoprotein E gene allele ε4- (APOE ε4-) (Piazza and Winblad 2016).

The mechanism underlying the development of amyloid-related imaging abnormality–edema/effusion (ARIA-E) and amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition (ARIA-H) during anti-amyloid treatment is not yet fully understood. Because antibodies remove 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). An anti-Aβ therapy that effectively maintains vascular Aβ clearance would allow vascular remodeling and might, over time, decrease the risk of such extravasation events (Sperling et al. 2012). This is consistent with experiences in previous and ongoing studies and with reported data from the long-term extension study of aducanumab treatment (Viglietta et al. 2016).

Understanding of the clinical significance of ARIA by study sponsors, investigators, and regulators has substantially evolved since ARIA events were first seen on MRI scans in

a Phase I clinical trial with bapineuzumab (Black et al. 2010). The accrued clinical evidence with gantenerumab and other N-terminus anti-amyloid antibodies has shown that ARIA events tend to occur early in treatment, are dose- and APOE ε4-dependent, and can be monitored by MRI and managed with dose intervention algorithms.

The Sponsor's experience with managing patients with ARIA findings and increasing understanding of the impact of such findings on patient clinical outcomes has resulted in the introduction of revised ARIA risk mitigation measures in studies with gantenerumab over time. Accordingly, ARIA management has shifted from more cautious management, where an ARIA-E finding resulted in treatment interruption regardless of intensity (Study WN25203 [double-blind]), to less restrictive management, where only moderate-severe intensity ARIA-E and symptomatic ARIA-E findings result in treatment interruption (Studies WN25203 and WN28745: OLE; Studies WN29922 and WN39658). Similarly, the cumulative number of ARIA-H findings that trigger treatment discontinuation was changed from 5 (Studies WN25203 and WN28745 [double-blind]) to 10 (Studies WN25203 and WN28745 [OLE]), to 15 (Studies WN29922 and WN39658). The revised management led to similar and acceptable safety profiles.
In Studies WN29922 and WN39658, safety reviews of unblinded data by an independent Data Monitoring Committee (iDMC) have not identified any new safety signal.

Taking into account the evolving experience with managing ARIA findings, including the finding that continued gantenerumab treatment during episodes of asymptomatic mild ARIA-E was not associated with clinically unfavorable outcomes, the Sponsor intends to examine the safety of continuing gantenerumab treatment through mild to moderate asymptomatic ARIA-E findings and to examine the safety of gantenerumab therapy in the presence of an increased number of ARIA-H microhemorrhages.

Study WN42171 will require an MRI scan documenting the absence of ARIA-E or evidence of disseminated leptomeningeal hemosiderosis prior to the first gantenerumab dose. If ARIA findings occur during the study, MRI monitoring, temporary dose holding, or permanent study drug discontinuation will be implemented according to an ARIA management plan, as described in Appendix 2.

Safety findings, including individual participant and aggregate data, will be reviewed on a regular basis by the Sponsor and by an iDMC. *In the event the iDMC which reviews safety in both the parent Studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.*

1.3.2.2 Injection-Site Reactions

The incidence of ISRs in gantenerumab-treated patients with up to the target gantenerumab dose (1200 mg SC Q4W) ranged from 36% (Study WN25203 OLE) to 38% (Study WN28745 OLE) as of 1 May 2019. All ISRs were non-serious, mostly mild

to moderate in intensity, and the majority resolved without treatment. The most common signs and symptoms of ISRs included injection-site erythema, redness, swelling, and itching. No patients discontinued study treatment due to ISRs.

1.3.2.3 Overall Benefit–Risk Summary

The benefit–risk assessment of gantenerumab treatment in Study WN42171 is based on the following:

- Gantenerumab has shown evidence of continuous reduction of the amyloid plaque component in up to 3 years of treatment and thus shows potential benefit in slowing the progression of AD.
- Findings from Study WN25203 (Klein et al. 2019), the PRIME study with aducanumab (Sevigny et al. 2016), and from the Phase II study with BAN2401 (Swanson et al. 2018) suggest that reduction in deposited amyloid is associated with a dose-related slowing of cognitive decline, providing additional support for the hypothesis that anti-amyloid treatment may be associated with a beneficial clinical effect.
- Results from the double-blind part of Studies WN25203 and WN28745, as well as from the *completed* OLEs Studies WN25203 and WN28745, showed that ARIA-E findings are mostly asymptomatic, non-serious, of mild severity, and do not require permanent cessation of treatment.
- No new safety signals have been identified from the ongoing Phase III studies with gantenerumab with doses of up to 510 mg Q2W or equivalent, which supports the safety of continued administration of gantenerumab uptitrated to the target dose in the current and planned studies, including Study WN42171.
- Study WN42171 will provide participants with the opportunity to extend treatment with gantenerumab beyond 2 years, thereby providing more information on the long-term safety, tolerability, and efficacy of gantenerumab in AD. Furthermore, the study will increase the overall number of participants exposed to gantenerumab and the patient-years of exposure and increase the understanding of the safety:efficacy profile. Analyzing the long-term safety, tolerability, and efficacy of gantenerumab is of critical importance to help clinicians make informed therapeutic decisions for participants.
- The design of Study WN42171 will allow participants with moderate asymptomatic ARIA-E and with any number of ARIA-H microhemorrhages to continue gantenerumab treatment. This is in line with the evolving understanding of the clinical significance of ARIA by the clinical trial Sponsors and medical community (see Section 3.3.4).
- An iDMC will evaluate safety data on a regular basis, including the incidence and nature of adverse events, serious adverse events, adverse events of special interest, ARIA-E, ARIA-H, and ISRs and will make appropriate recommendations (see Section 3.1.3). *In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies), evaluation of participant safety*

may be taken over by the Sponsor's IMC, with details documented in an IMC charter.

- The benefit–risk ratio of conducting Study WN42171 during the Coronavirus Disease 2019 (COVID-19) pandemic remains unchanged. This is supported by the nonclinical 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 gantenerumab administration could increase the risk of infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or more severe 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 Principal Investigator, 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.
- Based on the available information, no interactions between gantenerumab *or PET tracers* and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being investigated for the treatment of AD. Just as with other vaccinations (e.g., influenza), the administration of COVID-19 vaccines will be considered as a concomitant medication in this study.

Overall, the anticipated benefit–risk profile of gantenerumab supports open-label gantenerumab treatment in Study WN42171 for participants who completed either the double-blind or OLE part of parent Study WN29922 or WN39658.

2. OBJECTIVES AND ENDPOINTS

This study will evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658. Specific objectives and corresponding endpoints for the study are outlined below.

2.1 SAFETY OBJECTIVE

2.1.1 Primary Objective: Safety

The primary objective for this study is to evaluate the safety and tolerability of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events

- Physical examinations (including neurologic systems), vital signs, ECG, laboratory tests, and Columbia-Suicide Severity Rating Scale (C-SSRS)
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of ISRs
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

2.2 EFFICACY OBJECTIVE

2.2.1 Secondary Objective: Efficacy

The secondary objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Change over time in cognition *and/or* function as measured by the following:
  - Clinical Dementia Rating (CDR)
  - Mini-Mental State Examination (MMSE)
  - Alzheimer Disease Assessment Scale–Cognition, Subscale 11 (ADAS-Cog11) and Alzheimer Disease Assessment Scale–Cognition, Subscale 13 (ADAS-Cog13)
  - Verbal Fluency Task
  - Coding
  - Functional Activities Questionnaire (FAQ)
  - Alzheimer Disease Cooperative Study Group–Activities of Daily Living (ADCS-ADL)

2.2.2 Exploratory Objective: Efficacy

The exploratory objective for this study is to evaluate the efficacy of long-term gantenerumab administered by SC injection on the basis of the following endpoints:

- Change over time in:
  - Health-related quality of life, as assessed by the Quality of Life–Alzheimer's Disease (QoL-AD) scale
  - Behavioral and neuropsychiatric symptoms of AD, as measured by the Neuropsychiatric Inventory Questionnaire (NPI-Q)
  - Caregiver burden, as assessed by the Zarit Caregiver Interview for Alzheimer's Disease (ZCI-AD) scale
  - Elements of resource utilization, as assessed by the Resource Utilization in Dementia–Lite (RUD-Lite)

2.3 PHARMACOKINETIC OBJECTIVE

The exploratory pharmacokinetic (PK) objective for this study is to characterize the PK profile of gantenerumab administered by SC injection on the basis of the following endpoint:

- Plasma concentration of gantenerumab administered SC at specified timepoints

2.4 IMMUNOGENICITY OBJECTIVE

The immunogenicity objective for this study is to evaluate the immune response to gantenerumab administered by SC injection on the basis of the following endpoint:

- Prevalence of anti-drug antibodies (ADAs) at baseline and incidence of ADAs during the study

2.5 BIOMARKER OBJECTIVE

The exploratory biomarker objective for this study is to evaluate the long-term effects of gantenerumab administered by SC injection based on the following endpoints:

- 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
- CSF markers of disease over time in a subset of participants, including, but not limited to, $A\beta_{1-42}$, total tau (t-tau), and phosphorylated tau (p-tau)
- MRI-derived measurements over time, such as volumetric changes in whole brain, ventricles, hippocampus, or other structures; changes in functional brain connectivity; or changes in the integrity of white matter in all participants
- Blood and plasma markers over time

2.6 HEALTH STATUS UTILITY OBJECTIVE

The exploratory health status utility objective for this study is to evaluate the health status utility scores of participants treated with gantenerumab on the basis of the following endpoint:

- Health outcomes in participant and caregiver, as measured by EuroQol 5-Dimension Questionnaire (EQ-5D)

3. STUDY DESIGN

3.1 DESCRIPTION OF THE STUDY

3.1.1 Overview of Study Design

Study WN42171 is an open-label, multicenter, rollover study to evaluate the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658, either the double−blind or OLE part, as applicable (parent study). The blind to the study treatment allocation during the parent study will be maintained to protect study integrity.

Participants who have completed Study WN29922 or WN39658, either the double-blind or OLE part as applicable, will be eligible to participate in this study. Participants who discontinued early from study treatment during Study WN29922 or WN39658, regardless of the reason, will not be eligible for this study.

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow-up, until a day before the first dose in the Study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor, and it must be obtained before any study procedures in this study are performed.

The first administration of gantenerumab in this study will be as follows:

- For participants who completed the double-blind part and did not enter the OLE part of Study WN29922 or WN39658: The first administration of open-label gantenerumab should take place approximately 2 weeks after the last efficacy and safety visit of the double-blind part of the parent study (WN29922 or WN39658) and will be considered the OLE baseline visit (OLE Day 1).
- For participants who completed the double-blind part and the OLE part of Study WN29922 or WN39658, the first administration of gantenerumab in this study should take place approximately 2 weeks after the OLE Week 34 visit or the final dose visit in the Study WN29922 or WN39658 OLE. Participants who have a gap in their transition between the OLE part of the parent study (WN29922 or WN39658) and this study, for unforeseen reasons, will roll over to this study continuing the schedule of activities as per their last visit in the OLE part of the parent study (WN29922 or WN39658). Discussion with the Sponsor is recommended.

Participants with evidence of ARIA-E on the last per-protocol study MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, will be retained in the WN29922 or WN39658 study until the ARIA-E finding is resolved. They may then enroll in Study WN42171. *For those enrolling from the OLE part*, the first visit of the participants in Study WN42171 will be adapted according to the schedule of the visits of each participant in the parent study.

The data from the last visit in study WN29922 or WN39658 (e.g., final efficacy and safety visit of the double-blind part or last visit in the WN29922 or WN39658 OLE part) will be used as the data for the first visit in this study if the two visits take place within 4 weeks of each other. All cognitive scales, and the C-SSRS do not need to be repeated if they were performed within 6 months in the previous parent study. The MRI scan does not need to be repeated if performed within 6 months in the previous parent study (WN29922 or WN39658) and following the final study drug dose in the parent study. Vital signs and urine pregnancy test will have to be performed at the first visit in this study before dosing. MRI and urine pregnancy test results must be available before dosing.

In this study, participants who were in the active double-blind arm in the parent study (WN29922 or WN39658) will continue receiving open-label gantenerumab 510 mg SC Q2W, and those participants who were in the placebo double-blind arm will go through a full uptitration scheme while retaining the blinding to the previous treatment allocation. Details of the dosing scheme are described in Section 4.3.2. If there is a delay in a participant's transition between the OLE part of the parent Study (WN29922 or WN39658) and this study (for instance, due to delays in the approval of this study at a site) that goes beyond a reasonable time frame as determined by the Sponsor, the participant may be asked to start at the dose they were at previously when they completed the parent study and to perform a safety MRI before receiving the target dose. In this case, such decisions will be made after discussion with the Sponsor.

The dosing schedule and the schedule of activities will be different for participants, depending on whether they completed the OLE part of Study WN29922 or WN39658, which covers the uptitration phase for the participants in the placebo arm, or if they completed only the double-blind part. Details are described in Appendix 1.

Following baseline assessments (i.e., OLE Day 1 either in this protocol or in the parent protocol), each participant will be treated for *4* years. *The study duration has been extended from 2 to 4 years in order to collect more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure and to increase the overall number of participant-years of exposure, thus increasing understanding of gantenerumab's long-term safety and efficacy profiles. Unless participants are eligible and choose to enroll in an alternative gantenerumab OLE study that becomes available,* the final dose of study drug will be administered at OLE Week *206*. At the end of the treatment period, all participants will undergo an OLE Week *208* visit. Participants will be asked to come back for a follow-up visit at OLE Week *220 unless they are transitioning to an alternative gantenerumab OLE study that becomes available.*

Participants who discontinue study drug at any time during this study will be asked to complete an early termination visit 2 weeks after their final dose and also return for collection of safety data (except safety MRI) and limited efficacy data (i.e., secondary endpoints) (see Section 4.6.1).

Participants who do not meet the criteria for participation in this study (screening failure) may be re-screened. The investigator will record reasons for screening failure in the screening log (Section 4.5.1).

3.1.2 Substudies

The substudies associated with Study WN42171 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, two optional substudies are associated

with Study WN42171: a longitudinal amyloid PET substudy and a longitudinal tau PET substudy.

The amyloid and tau PET assessments will enable 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 (Genentech Tau Probe 1; an investigational radioligand for in vivo imaging of tau protein aggregates) in participants with AD.

The collected PET data are expected to help in understanding the effects of gantenerumab on amyloid and tau pathology over time as well as the relationship between changes in florbetaben/flutemetamol/[^{18}F]GTP1-PET and changes in other endpoints in Study WN42171.

Two optional substudies associated with this protocol may be introduced.

In one of them, post-mortem brain tissue may be obtained from participants for evaluation of the effect of long-term gantenerumab therapy on the brain.
The opportunity to donate post-mortem brain tissue may be discussed with participants.

In the other one, digital tools that assess the disease progression of the participants may be tested for validation and for other exploratory purposes.

Interested participants would be provided with additional details. Any further procedures, with respect to the optional substudies, will be governed by a separate consent form and separate substudy protocol document.

3.1.3 Independent Data Monitoring Committee

The iDMC will evaluate participant safety 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, including efficacy data if necessary, at regular intervals during the study. It is anticipated that these assessments will occur approximately every 3 months *or as detailed in the iDMC charter*. At the time of each review, the iDMC will make appropriate recommendations (e.g., the study should continue as planned, the safety risk management should be modified, the protocol should otherwise be amended, and enrollment should be held pending further safety evaluations).

Decisions will be made after considering 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.

In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and Study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety *may* be taken over by the Sponsor's IMC, with details documented in an IMC charter.

3.2 END OF STUDY AND LENGTH OF STUDY

The end of this study is defined as the date when the last participant, last visit, occurs or the date at which the last data point required for statistical analysis or safety follow-up is received from the last participant, whichever occurs later. The end of the study is expected to occur by the end of *2026*.

In addition, the Sponsor may decide to terminate the study at any time.

The total length of this study from baseline visit (OLE Day 1 in either the Study WN42171 protocol or in the parent protocol) to the end of the study (including the follow-up visit) is expected to be approximately *4* years and 3 months. Following uptitration, participants will receive up to *86* doses of gantenerumab 510 mg Q2W. Participants who did not participate in the OLE part of the parent study (WN29922 or WN39658) will also go through an uptitration scheme in the WN42171 study with a duration of at least 34 weeks.

3.3 RATIONALE FOR STUDY DESIGN

3.3.1 Rationale for Gantenerumab Dose and Titration Schedule

All participants will receive a target dose of 510 mg gantenerumab SC Q2W, which is the same as the target dose received in the parent Study (WN29922 or WN39658). Participants who will be receiving gantenerumab for the first time in the WN42171 study will follow a titration schedule with a low starting dose and gradual increase in dosing that is expected to reduce the risk of ARIA-E for both apolipoprotein E (*APOE*) carriers and non-carriers, which was also followed in the WN29922 and WN39658 studies.

3.3.2 Rationale for Participant Population

Participants with AD who completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, will be eligible to participate in this study in order to evaluate the safety, tolerability, and efficacy of long-term gantenerumab administration. Additionally, participants in the placebo double-blind arm in the parent studies will get exposure to potentially active treatment.

3.3.3 Rationale for Study Treatment Duration

3.3.3.1 *Rationale for the First 2-Year Duration*

In order to collect safety, tolerability, and efficacy data for long-term gantenerumab administration, this study will provide open-label gantenerumab to participants who

completed study WN29922 or WN39658, either its double-blind or OLE part, as applicable, for 2 years starting from baseline (OLE Day 1 in either this protocol or the parent protocol). With the 2-year duration, participants in the placebo double-blind arm in the parent studies (WN29922 or WN39658) will receive the full 2 years of therapy, like their co-participants who were in the active double-blind arm.

3.3.3.2 *Rationale for the Subsequent 2-Year Duration*

The extension of the study treatment duration from 2 to 4 years will allow the collection of more information on the long-term safety and tolerability of gantenerumab in AD and its efficacy in the context of long-term exposure. In addition, this will increase the overall number of participants exposed to gantenerumab and participant-years of exposure, thus increasing understanding of gantenerumab's long term safety and efficacy profiles.

3.3.4 Rationale for ARIA Management Rules

In previous studies with gantenerumab, the Sponsor used the Barkhof scale (Barkhof et al. 2013) to assess the radiological severity of ARIA-E. In this study, the Sponsor plans to use the Bioclinica 5-point scale (Bracoud et al. 2017), which is a simpler scale for assessing ARIA-E severity that is based on a single overall assessment of ARIA-E extent. The Bioclinica 5-point scale is easier for clinicians to use than the Barkhof scale. The Bioclinica scale is commonly used in other clinical trials that are testing anti-amyloid antibodies (Ferrero et al. 2016).

Most cases of ARIA-E occur as an imaging finding alone, without any detectable clinical symptoms (see Gantenerumab Investigator's Brochure safety summary section). As detailed in Appendix 2, ongoing dosing of gantenerumab will occur in cases where ARIA-E is asymptomatic with a low or moderate imaging severity; in such cases, more frequent MRI surveillance (Q4W) will be mandatory. Any ARIA-E associated with symptoms (see definition of symptomatic ARIA-E in Section 5.3.5.2 and Appendix 2), regardless of radiographic severity, will require temporary withholding of study drug administration, until symptoms and ARIA-E findings resolve. The goal, in the context of this carefully controlled study with strict safety monitoring, is to minimize unnecessary study drug interruption, which could itself have a negative impact upon participants. Because of the safety monitoring and the regular review of safety data by the iDMC *or IMC (in the event that the iDMC is no longer required)*, this ARIA management strategy has a neutral impact upon participant risk.

3.3.5 Rationale for Biomarker Assessments

The following biomarker assessments will be used to investigate the effects of gantenerumab on the underlying pathology of AD in the participant population: CSF, plasma, and RNA (Section 4.5.7.3); PET imaging (Section 4.5.11); and brain volumetry, connectivity, and fiber tract integrity (Section 4.5.10).

Exploratory research on potential safety biomarkers may be conducted to support future drug development, including guidance for safety risk management.

3.3.5.1 Cerebral Spinal Fluid Biomarkers

Amyloid plaque deposition, neurofibrillary tangle formation, and neuronal degeneration are known pathologic features of AD. Decreased CSF Aβ1−42 and elevated CSF t-tau and p-tau are considered a biochemical signature of AD. Accumulating evidence suggests that low CSF Aβ1−42 reflects underlying amyloid plaque pathology, whereas increased t-tau and p-tau levels 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 have not yet been validated as surrogate markers for clinical efficacy, there is some evidence that anti-Aβ treatments may cause changes in these biomarkers. A neuropathologic study of patients with AD (Study AN1792) suggests that active amyloid immunotherapy ameliorates neurite abnormalities and tau pathology through decreased tau phosphorylation (Serrano-Pozo et al. 2010). In a pooled analysis of CSF data from two Phase II trials with bapineuzumab in patients with mild to moderate AD, a decrease in both p-tau and t-tau levels relative to baseline was observed in the bapineuzumab group after 12 months of therapy (Blennow et al. 2010). These findings were confirmed in two Phase III studies with bapineuzumab (Sperling et al. 2012) as well as in Study WN25203 with gantenerumab. In Study WN25203, CSF biomarkers were analyzed over the 2-year period for changes in multiple proteins, including $A\beta_{1\text{-}42}$, t-tau, p-tau, and neurogranin. 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 has been demonstrated with these therapies in clinical trials yet, changes in these biomarkers provide meaningful information about the PD 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 in this study. Because gantenerumab is expected to clear amyloid from the brain, levels of CSF $A\beta_{1-42}$ will also be measured.

3.3.5.2 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 patients with AD (e.g., enlarged ventricles, decreased cortical thickness, decreased total brain volume, and hippocampal atrophy), and there is evidence for strong correlations between these imaging biomarkers and functional cognitive measures (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 in this study. 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 patients 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 patients with brain amyloid deposition (Pittsburgh Compound-B+PET scans). Alteration of the decreased brain functional connectivity has been shown using therapeutic interventions such as memantine (Lorenzi et al. 2011) or donepezil in patients with AD (Goveas et al. 2011; Solé-Padullés et al. 2013). Increased brain functional connectivity was found after just 3 months of treatment with donepezil, which correlated with changes in cognitive measures such as the ADAS-Cog (Goveas et al. 2011; Solé-Padullés et al. 2013). Therefore, therapeutic interventions, which act to remove Aβ from the brains of patients with AD, may help to reverse the altered functional connectivity 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 patients 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 groups with AD compared with healthy controls, presumably owing to increased white matter injury in patients 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.

3.3.6 Rationale for Pharmacokinetic Sampling

A sparse sampling schedule is being utilized to minimize participant burden while providing 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 AD, as appropriate.

4. MATERIALS AND METHODS

4.1 PARTICIPANTS

Any participant who has completed Study WN29922 or WN39658, either the double-blind or OLE part, as applicable, can be enrolled in this study if they meet the inclusion/exclusion criteria set out below. This should lead to no more than 2032 participants with AD enrolled in Study WN42171, dependent on the number of eligible participants completing the parent Studies (WN29922 and WN39658) and who consent to Study WN42171.

4.1.1 Inclusion Criteria

Participants must meet the following criteria for study entry:

- Signed Informed Consent Form by the participant with AD and/or the legal authorized representative as per local requirements
- Completed Study WN29922 or WN39658, either its double-blind part (participants have reached the 510 mg Q2W dose schedule by the time of completion) or OLE part (participants have received at least 3 doses of 510 mg Q4W), and did not discontinue study drug early
- Ability to comply with the study protocol
- Willingness and ability to complete all aspects of the study (including MRI).
- The participant should be capable of completing assessments either alone or with the help of the caregiver.
- Availability of a person (referred to as the “caregiver” throughout this protocol) who:
  - 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 caregiver participate throughout the duration of the study.

- For women of childbearing potential: agreement to remain abstinent (refrain from heterosexual intercourse) or use contraception as defined below:
  - Women must remain abstinent or use contraceptive methods with a failure rate of $<1\%$ per year during the treatment period and for at least 16 weeks after the final dose of gantenerumab.
  - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and is not permanently infertile due to surgery (i.e., removal of ovaries, fallopian tubes, and/or uterus) or another cause as determined by the investigator (e.g., Müllerian agenesis). The definition of childbearing potential may be adapted for alignment with local guidelines or regulations.
  - 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 adequate methods of contraception. If required per local guidelines or regulations, locally recognized adequate methods of contraception and information about the reliability of abstinence will be described in the local Informed Consent Form.
- 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.

4.1.2 Exclusion Criteria

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

- Pregnant or breastfeeding, or intending to become pregnant during the study or within at least 16 weeks after the final dose of study drug

  Women of childbearing potential must have a negative urine pregnancy test at the final visit of the parent study.
- Prematurely discontinued from Study WN29922 or WN39658, either its double-blind or OLE part, as applicable, or from study drug, for any reason
- Any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues to receive study treatment
- Received any investigational treatment other than gantenerumab during or since completion of Study WN29922 or WN39658, either its double-blind or OLE part, as applicable
- Evidence of disseminated leptomeningeal hemosiderosis (i.e., more than three focal leptomeningeal hemosiderosis)
- Evidence of intracerebral macrohemorrhage
- Use of prohibited medication (see Section 4.4.2)
- Evidence of ARIA-E on the last MRI scan report in Study WN29922 or WN39658, either its double-blind or OLE part, as applicable

  Participants should remain in the parent study, as governed by that protocol, and may enroll in this study once the ARIA-E is resolved.

4.2 METHOD OF TREATMENT ASSIGNMENT AND BLINDING

4.2.1 Treatment Assignment

This is a non-randomized, open-label study. An interactive voice or web-based response system (IxRS) will be used to manage participant enrollment and drug supply. After initial written informed consent has been obtained the study site may obtain the participant's identification number. After all screening procedures and assessments have been completed, and eligibility has been established for a participant, the study site will obtain the participant's treatment assignment from the IxRS.

Participants randomized to the active treatment arm in the parent study (WN29922 or WN39658) will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants randomized to the placebo arm in the parent study (WN29922 or WN39658) will have to go through at least 34 weeks of uptitration. Participants, sites, and Sponsor will remain blinded to previous treatment allocation in the parent study (WN29922 or WN39658) to protect study integrity.

4.2.2 Blinding

To protect study data integrity and to aid the assessment of the long-term effects of gantenerumab, study site personnel and participants will be blinded to previous treatment assignment in the parent studies (WN29922 or WN39658). The Sponsor and its agents will also be blinded to previous treatment assignment, at least until unblinding of the parent studies (WN29922 and WN39658), which will happen while this study is ongoing, with the exception of individuals who require access to participant's treatment assignments to fulfill their job roles during a clinical trial. These roles include the unblinding group responsible, clinical supply chain managers, operational assay group personnel, IxRS service provider, and iDMC members.

Pharmacokinetics and immunogenicity samples will be collected from all participants, regardless of the treatment assignment. Laboratories responsible for performing study drug PK and ADA assays will be unblinded to participants' treatment assignments. Baseline immunogenicity samples will be analyzed for all participants.

If unblinding is necessary for a medical emergency (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. The investigator is not required to contact the Medical Monitor prior to breaking the treatment code; however, the treatment code should not be broken except in emergency situations.

If the investigator wishes to know the identity of the study drug for any reason other than a medical emergency, he or she should contact the Medical Monitor directly.
The investigator should document and provide an explanation for any non-emergency unblinding. If the Medical Monitor agrees to participant unblinding, the investigator will be able to break the treatment codes by contacting the IxRS.

As per health authority reporting requirements, the Sponsor's Drug Safety representative will break the treatment assignment code for all serious, unexpected suspected adverse reactions (see Section 5.7) that are considered by the investigator or Sponsor to be related to study drug. The participant may continue to receive treatment, and the investigator, participant, and Sponsor personnel, with the exception of the Drug Safety representative and personnel who must have access to participant treatment assignments to fulfill their roles (as defined above), will remain blinded to treatment assignment.

4.3 STUDY TREATMENT AND OTHER TREATMENTS RELEVANT TO THE STUDY DESIGN

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

4.3.1 Gantenerumab and Placebo

The Sponsor will supply gantenerumab and placebo, as required for the uptitration period, 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 the Gantenerumab Investigator's Brochure.

4.3.2 Study Treatment Dosage, Administration, and Compliance

During the WN42171 study, participants previously randomized to the active treatment arm and those who were previously randomized to placebo and have completed OLE uptitration in the parent study (WN29922 or WN39658) will continue to be administered the study drug every 2 weeks (Q2W administration of 510 mg SC gantenerumab). Participants previously randomized to the placebo arm who did not participate in the OLE part of the parent study (WN29922 or WN39658) will be required to undergo the uptitration scheme of 34 weeks. Participants who completed the OLE part of the parent study (WN29922 or WN39658), will continue the schedule of activities as per their OLE Day 1 visit in the parent study (WN29922 or WN39658).

In order to maintain the previous study treatment blinding (the Sponsor, investigator, and participant), all participants will be dosed every 2 weeks as illustrated in Table 1 . A safety MRI should be performed before each uptitration to ensure the participant can be safely uptitrated to the next dose.

To ensure blinding to previous treatment, IMP will be administered as one 0.8-mL and two 1.7-mL injections for the 120-mg dose or as two 1.7-mL injections for the 255-mg dose and 510-mg dose, respectively, SC to the abdomen. Injections may contain active gantenerumab or placebo to ensure the correct total dose of active gantenerumab at each visit (see Table 1). Refer to the pharmacy manual for detailed instructions on drug preparation, storage, and administration.

Note: A minimum of 3 doses during each dosing step must be administered before the participant is eligible for uptitration, subject to the results of a pre-uptitration safety MRI. **A dose is defined as two consecutive dosing visits (one with an odd dose number and one with an even dose number,** see Table 1). A participant may still be eligible for uptitration even if these requirements are not met, provided that they have been administered IMP at 3 odd dosing visits at a given dose level (see Table 1).

After OLE Week 34 (i.e., beyond the time frame considered in Table 1), all participants who have completed the uptitration will receive two 1.7-mL injections of active gantenerumab for the 510-mg dose at each subsequent 2-week visit.

At applicable sites, study treatment 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.

Details on treatment administration (e.g., dose and timing) should be noted on the Study Drug Administration electronic Case Report Form (eCRF). Cases of accidental overdose or medication error along with any associated adverse events should be reported as described in Section 5.3.5.13.

Guidelines for treatment interruption or discontinuation for participants who experience selected adverse events are provided in Section 5.

Table 1 Gantenerumab Dosing Design for Participants Who Did Not Participate in the OLE Part of the Parent Study (WN29922 or WN39658)

Visit		OLE Day 1	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	OLE Wk 24	OLE Wk 26	OLE Wk 28	OLE Wk 30	OLE Wk 32	OLE Wk 34
Dose Number Within Study WN42171		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	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 + 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; OLE = open-label extension; P = placebo; Q2W = every 2 weeks; Q4W = every 4 weeks; Wk = week.

4.3.3 PET Tracers

All participants who are enrolled in the PET substudies will be assessed by PET imaging using the same PET ligand as per the parent study (florbetaben or flutemetamol for the amyloid PET and [^{18}F]GTP1 for the tau PET substudy). According to European Union (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.

4.3.4 Investigational Medicinal Product Accountability

All IMPs required for completion of this study will be provided by the Sponsor. The study site will acknowledge receipt of IMPs supplied by the Sponsor, using the IxRS to confirm the shipment condition and content. Any damaged shipments will be replaced.

IMPs will either be disposed of at the study site according to the study site's institutional standard operating procedure or be returned to the Sponsor with the appropriate documentation. The site's method of destroying Sponsor-supplied IMPs must be agreed to by the Sponsor. The site must obtain written authorization from the Sponsor before any Sponsor-supplied 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.

4.3.5 Continued Access to Gantenerumab

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

A participant will be eligible to receive Roche IMP 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 Roche IMP 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 Roche IMP gantenerumab after completing the study if any of the following conditions are met:

- The Roche IMP 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 IMP or data suggest that the IMP is not effective for AD.
- The Sponsor has reasonable safety concerns regarding the IMP as treatment for AD
- Provision of the Roche IMP is not permitted under the laws and regulations of the participant's country.

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

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

4.4 CONCOMITANT THERAPY

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a participant in addition to protocol-mandated treatment from 3 months prior to first administration of study drug in Study WN42171 to the OLE final follow-up visit. All such medications (including name, dose, administration schedule, start and end dates) used by the patient during Study WN42171 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., AChEIs, memantine, and/or medical food supplements, where approved) with the exception of GV-971. Participants who have received GV-971, are currently 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) should be captured on the eCRF.

Adding a new medication or changing the dose of a medication during the study 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. Doses are expected to remain stable after baseline:

- Anticonvulsant medications
- Selective serotonin reuptake inhibitors for the treatment of depressive symptoms

- Over-the-counter and/or herbal medications, food additives, 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)
- Use of short-acting (non-extended release) opioid medications for pain
- Use of benzodiazepines, including alprazolam, lorazepam, oxazepam, triazolam, or temazepam, or short-acting hypnotic medication (e.g., zolpidem)
- A dose of benzodiazepine for pre-surgical and pre-imaging sedation at appropriate visits if allowed by the Ethics Committee (EC) or Institutional Review Board (IRB)
- Use of centrally acting antihistamine medications
- 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. However, for any such use it is recommended to prospectively seek advice from the Medical Monitor, and study drug *should be temporarily interrupted whilst anticoagulation therapy is ongoing.*

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

The administration of COVID-19 vaccines, just as with other vaccinations (e.g., influenza) will be considered as a concomitant medication. Based on the available information, no interactions between gantenerumab or PET tracers and the COVID-19 vaccines are expected to occur, and no other safety concerns have been identified that would prohibit the vaccination of participants enrolled in the studies where gantenerumab is being investigated for the treatment of AD. However, the published safety data for COVID-19 vaccines show that overlapping adverse events between medicines such as gantenerumab and the vaccine can occur: the timing and the nature of local injection reactions (occurring within 24 hours) as well as of systemic injection reactions may be similar for both products. To facilitate the correct clinical assessment of any adverse events and to continue correct attribution of adverse events related to study drugs (gantenerumab and PET tracers) or to the vaccination, namely of local and systemic reactions following the injections, the Sponsor recommends to vaccinate study participants at least 24–48 hours after an injection of study drug. Similarly, vaccination in the 48 hours preceding a study drug administration should also preferably be avoided. However, the timing of the study visits and study drug administration should not be unduly postponed because of a vaccination.

4.4.2 Prohibited Therapy

The following medications are prohibited at study start and during the entire period of study participation. Participants who start these medications during the study may be withdrawn from study treatment:

- Any 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 or approved to prevent or postpone cognitive decline within 1 year of screening, except for gantenerumab
- Any other investigational treatment or any other treatment with an investigational monoclonal antibody within 5 half-lives or 4 months prior to screening, whichever is longer
- Any previous administration of GV-971
- Anti-coagulation medications
  - 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 *study drug should be temporarily interrupted whilst anticoagulation therapy is ongoing.*

The following medications *should preferably be avoided* in this study *although they* are *not strictly prohibited*:

- Stimulant medications (amphetamine, methylphenidate preparations, or modafinil) throughout the study
- Typical antipsychotic or neuroleptic medication
- Atypical antipsychotic medications
- Chronic use of opiates or opioids (including long-acting opioid medication)
- Chronic use of benzodiazepines, barbiturates, or hypnotics

If possible, use should be limited to intermittent short-term use. Consideration should be made as to whether clinically appropriate to interrupt the medication 2 days or at least 5 half-lives (whichever is longer) prior to any neurocognitive assessment due to their psychoactive effects.

4.5 STUDY ASSESSMENTS

The schedule of activities to be performed during the study is provided in Appendix 1. All activities should be performed and documented for each participant.

At applicable sites, certain study assessments may be performed by a mobile nursing (MN) professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study. The Sponsor will select a healthcare company that will be responsible for providing MN services for participating sites (the MN vendor). The MN vendor is responsible for ensuring that all MN 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 MN services are appropriate for a participant and the participant gives written informed consent to participate in MN visits, the MN network will communicate with the participant and the participant's site. MN visits will be scheduled on specified visit days, to allow for relevant assessments to be performed by the MN professional. The schedule of activities (see Appendix 1) specifies the assessments that may be performed by an MN professional.

4.5.1 Informed Consent Forms and Screening Log

Informed consent should be obtained from participants while they are in the parent study (WN29922 or WN39658) including in the safety follow up, until a day before the first dose in the study WN42171. In special situations, informed consent can be obtained at a later timepoint upon providing an appropriate rationale to the Sponsor. Written informed consent for participation in the study must be obtained before performing any study-related procedures. Informed Consent Forms for enrolled participants and for participants who are not subsequently enrolled will be maintained at the study site.

All screening evaluations must be completed and reviewed to confirm that participants meet all eligibility criteria before enrollment. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

4.5.2 Baseline Definition and Assessments

For participants who completed the double-blind part and did not enter the OLE part of study WN29922 or WN39658: The first dosing visit in this study will be considered as baseline (OLE Day 1), and the final efficacy and safety visit assessment of the parent Study (WN29922 or WN39658) will be considered as baseline assessment if occurring within a specific timeframe.

For participants who completed the double-blind part and the OLE part of study WN29922 or WN39658: the baseline visit will be the OLE Day 1 visit of the parent study (WN29922 or WN39658). This group of participants will roll over to study WN42171 upon the completion of their uptitration. The first visit in this study should take place approximately 2 weeks after the OLE Week 34 visit or the last dose visit in the parent study (WN29922 or WN39658) OLE.

On the day of the first dose of gantenerumab in study WN42171, if results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks are available, they do not have to be repeated. For C-SSRS, and cognitive scale results, the time interval is 6 months. MRI scan does not need to be repeated if performed within 6 months in the parent study and following the final study drug dose in the parent study. Vital signs, urine pregnancy test for women of childbearing potential, collection of adverse events, and review of concomitant medications have to take place before each dose administration. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study, including those required for ARIA-E follow up.

4.5.3 Medical History, Baseline Conditions, Concomitant Medication, and Demographic Data

Medical history and demographic data as collected in the parent Study WN29922 or WN39658 will be used in this study and should include clinically significant diseases, surgeries, cancer history (including prior cancer therapies and procedures), reproductive status, smoking history, and use of alcohol and drugs of abuse. Medical history and demographic data will be automatically transferred into the study WN42171 eCRF. In addition, ongoing concomitant medications will automatically be transferred from the parent study (WN29922 or WN39658) to study WN42171. All changes to medications during the study (e.g., prescription drugs, over the counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) should be recorded in the eCRF. Changes in medical history will be collected once after completion of the double-blind part in the parent study (WN29922 or WN39658) and before OLE Day 1 either in the parent study or in study WN42171.

Demographic data will include age, sex, and self-reported race/ethnicity.

Because 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).

4.5.4 Physical Examinations

A complete physical examination, performed at specified visits as per the schedule of activities (Appendix 1), should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated. Conditions reported as part of the medical history or adverse events in the parent study do not need to be re-entered.

Limited, symptom-directed physical examinations should be performed at specified visits and 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 OLE Day 1, at OLE Week 104*, at OLE Week 208,* or at the OLE early termination visit, at every visit at which creatinine clearance is tested, and at any other visit as deemed necessary by the investigator. Height will be obtained at the first dosing visit only.

The physical examination does not have to be repeated at OLE Day 1 or at the first dosing visit in the WN42171 study if the last examination performed in the parent study (WN29922 or WN39658) occurred within the previous 4 weeks.

4.5.5 Vital Signs

Vital signs will include measurements of respiratory rate, pulse rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. Any abnormalities recorded in the parent studies do not need to be re-entered on the Study WN42171 eCRF. At subsequent visits, record new or worsened clinically significant abnormalities on the Adverse Event eCRF.

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 MN professional.

4.5.6 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 4.5.6.14.

Whenever possible, there should be consistency in the rater and caregiver who complete the scales for each participant throughout the duration of this study and also between this study and the parent study. Potential raters will receive training and be approved by the rating scale contract research organization 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, 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 CDR, a secondary efficacy outcome measure in this trial, involves subjective judgment, the adequacy of participant and caregiver 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 CDR 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).

During OLE Day 1 or the visit of the first study drug administration in Study WN42171, scale assessments do not have to be repeated if the last assessments performed in the parent study WN29922 or WN39658 occurred within 6 months.

4.5.6.1 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 CDR–Sum of Boxes (CDR-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 caregiver).

As much as is feasible, the CDR should be administered to an individual participant by the same assessor throughout the study, preferably the same assessor as in the parent study, and that assessor should not perform the MMSE, ADAS-Cog, Verbal Fluency Task, Coding, FAQ, or 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 caregiver interview but before ADAS-Cog, MMSE, Verbal Fluency Task, Coding, and other scales are completed. Nevertheless, on OLE Day 1, on OLE Week 52, on OLE Week 104*, on OLE Week 156, and on OLE Week 208,* the CDR rater cannot perform other scales than the CDR. In addition, the CDR rater should <u>not</u> be involved in safety assessments and especially should <u>not</u> receive information about any ARIA findings.

4.5.6.2 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.

4.5.6.3 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.

4.5.6.4 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).

4.5.6.5 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.

4.5.6.6 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.

4.5.6.7 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 activities of daily living (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.

4.5.6.8 Zarit Caregiver Interview for 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 caregiver without involvement from the site staff. It has a 4-week recall period.

4.5.6.9 Quality of Life–Alzheimer's Disease

The QoL-AD was developed to assess quality of life (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 health-related QoL. 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 caregiver will also complete the caregiver version of the questionnaire to enable proxy responses from the caregiver.

4.5.6.10 EQ-5D

The 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 caregiver (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 caregiver is asked to rate his or her own health-related QoL.

4.5.6.11 Resource Utilization in Dementia Scale

The 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 caregiver sociodemographics in addition to working status and effect on productivity will be collected. The amount of informal care will be collected according to three types of care: personal ADL, 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.

4.5.6.12 Neuropsychiatric Inventory Questionnaire

The NPI-Q (Kaufer et al. 2000) was developed to assess a wide range of behaviors encountered in patients with dementia, 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 caregiver's distress portion of the scale will not be used in this study.

4.5.6.13 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, FAQ, QoL-AD, EQ-5D, RUD-Lite, NPI-Q, $ZCI\text{-}AD,$ and CSSR-S.

4.5.6.14 Treatment Period Assessments

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 caregiver input, should be completed before any invasive safety assessments.
- Vital sign measurements, physical examination, ECGs, blood draws for clinical laboratory assessments, PK, ADA, plasma biomarker sampling, and urine samples are recommended to be conducted following scale assessments and must be performed prior to study drug administration.

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

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

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; EQ-5D=EuroQol-5-Dimension Questionnaire; 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 for 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.

On each dosing day, after all assessments prior to dosing have been completed (see the schedule of activities in Appendix 1), gantenerumab and matching placebo where applicable during uptitration will be administered SC at room temperature.

For participants who completed the double-blind part and did not enter the OLE part of parent Study (WN29922 or WN39658): Participants should be observed for a minimum of 2 hours for the first eight administrations. Starting at the ninth administration, participants should be observed for a minimum of 1 hour.

For participants who completed the double-blind part and the OLE part of parent Study (WN29922 or WN39658): Participants should be observed for a minimum of 1 hour.

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 caregivers 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 ±3 days of the protocol-specified date in the schedule of activities (Appendix 1). It is recommended not to administer more than 2 dosing visits (e.g., 2×510 mg Q2W) within 28 days. At every visit, participants should return to the initial planned visit schedule defined as per the baseline visit (OLE Day 1).

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 one 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.

4.5.7 Laboratory, Biomarker, and Other Biological Samples

Samples for the following laboratory tests will be sent for analysis:

- Serum chemistry panel: AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, serum creatinine (and creatinine clearance calculated by the central laboratory). Hemoglobin A_{1c} (HbA_{1C}), glucose, insulin, C-reactive protein, folic acid, and vitamin B-12 will also be assessed according to the schedule of activities (Appendix 1).
- Coagulation: prothrombin time
- Thyroid function testing: thyroid-stimulating hormone, thyroxine (T4), and free T4
- Lipids: cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides
- Hematology: WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells)
- Urinalysis

  At the OLE Day1 visit or at the visit of the first study drug administration in Study WN42171, if deemed necessary by the investigator, urinalysis may 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 pregnancy test

  Urine pregnancy tests will be performed at each dosing visit (prior to dose administration) and at the safety follow up visit for women of childbearing potential (including those who have had a tubal ligation) and at the site for any other female participants if required by local regulations. 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.

During the OLE Day 1 visit or at the visit of the first study drug administration in Study WN42171, the above laboratory assessments (excluding urine pregnancy test) do not have to be repeated if the last assessments performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

4.5.7.1 Pharmacokinetic Samples

Plasma 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 practicable (e.g., at an unscheduled visit or the next study

visit) once the site becomes aware of the occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria.

Samples will not be analyzed 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 and for the quantification of specific gantenerumab glycan species.

Cerebrospinal Fluid Samples

For participants who were randomized in parent study (WN29922 or WN39658) based on CSF Aβ and tau level results who undergo lumbar puncture in the schedule of activities, an aliquot of CSF obtained by lumbar puncture, described in Section 4.5.7.3, will be allocated for the measurement of gantenerumab concentration. Unused sample material may also be used for the purposes of current assay improvement.

4.5.7.2 Plasma Samples for Immunogenicity Analysis

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 analyzed for antibodies to gantenerumab.

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

4.5.7.3 Biomarker Samples

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 4.5.14).

Cerebrospinal Fluid and Serum Biomarkers

CSF samples and matching serum samples will be obtained from participants who were randomized in the parent Study (WN29922 or WN39658) based on CSF Aβ and tau level results. CSF samples will be collected during the study at different timepoints for monitoring the levels of Aβ and tau as well as other CSF biomarkers.

The serum samples collected at every timepoint at which a CSF sample is collected may be used to determine parameters that allow the assessment of blood-brain barrier status and/or inflammatory processes in the brain, such as the 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 processing 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 CSF gantenerumab levels
- Analysis of biomarkers in CSF, including $A\beta_{1-42}$, t-tau, p-tau, and other exploratory CSF biomarkers

Samples may also be used to support the development of biomarker assays for diagnostic use.

Plasma Biomarkers

Plasma samples will be collected at different timepoints (see Appendix 1) from every participant who has consented to participate in the study. Samples will be used to evaluate exploratory plasma biomarkers in peripheral blood, which may include, but will not be limited to Aβ, tau, neurofilament, and neurogranin.

An additional plasma sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

RNA Biomarkers

Blood samples at different timepoints (see Appendix 1) will be obtained for RNA extraction from every participant who has consented to participate in the study, at OLE Day 1 (only if an RNA sample has not been collected at the final efficacy and safety visit of the parent study [WN29922 or WN39658]), at OLE Week 104 visit, *and OLE Week 208 visit* or OLE early termination visit of this study.

The sample may be used to evaluate clusterin messenger RNA and other exploratory genetic markers in peripheral blood.

Additionally, an RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

SAMPLING PROCEDURES AND STORAGE

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

Roche may keep information about test results, medical history, and demographic information for all participants also from the parent studies for future development of diagnostic tests related to Aβ, *APOE* genotype, and AD, as well as additional analyses.

Unless the participant gives specific consent for his or her leftover samples to be stored for optional exploratory research (Section 4.5.14), biological samples will be destroyed no later than the time of completion of the final Clinical Study Report, with the following exceptions:

- Plasma samples collected for PK or immunogenicity analysis may be needed for additional immunogenicity characterization and for PK or immunogenicity assay development and validation, therefore, these samples will be destroyed no later than 5 years after the final Clinical Study Report has been completed.
- Blood, plasma, serum, and CSF samples collected for biomarker research and biomarker assay development 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)

When a participant withdraws from the study, samples collected prior to the date of withdrawal may still be analyzed, unless the participant specifically requests that the samples be destroyed or local laws require destruction of the samples. However, if samples have been tested prior to withdrawal, results from those tests will remain as part of the overall research data.

Data arising from sample analysis, including data on genomic variants, will be subject to the confidentiality standards described in Section 8.4.

Given the complexity and exploratory nature of exploratory biomarker analyses, 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.

4.5.8 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.

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.

At the OLE Day 1 visit or at the visit of the first study drug administration in Study WN42171, ECG does not have to be repeated if the last ECG performed in the parent studies WN29922 or WN39658 occurred within 4 weeks.

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.

4.5.9 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 from the parent study will be used, 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 caregiver during the study visit.

4.5.10 Brain Magnetic Resonance Imaging

MRI should be performed using 1.5-T or 3.0-T scanners. Whenever possible, the same scanner should be used for an individual participant for the full duration of the study. The MRI obtained at baseline and/or at the final efficacy and safety visit in the parent study may be used as a baseline measure of structural brain volumes and as baseline information for the PET substudies (see the schedule of activities in Appendix 1).

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

The MRI from the final efficacy and safety visit of the parent study (WN29922 or WN39658) will be used to determine whether there are any significant findings (e.g., presence of mass lesions, etc.) that may preclude the participant's safe participation in and completion of this study. Similarly, the MRI obtained at the end of the titration in participants who completed the parent study OLE will be used to determine if any significant findings preclude participation in Study WN42171. In case of an ARIA-E finding, the participant should undergo Q4W MRI monitoring until the ARIA-E is resolved. Participants may enroll in study WN42171 once the ARIA-E is resolved using their last MRI in the parent study (WN29922 or WN39658) for eligibility purposes.

MRI will be used during the study to help assess safety, such as the occurrence of ARIA. Additional unscheduled MRI scans may be performed to better understand if relevant CNS adverse events (such as increased confusion) are occurring in the context of ARIA or to follow up 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 fluid-attenuated inversion recovery 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.

Magnetic resonance imaging 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.

MRI scans will be reviewed by a central MRI core laboratory, which will perform the diagnostic reads and assessments 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 the dosing visit that the MRI corresponds to (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.

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 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 5.1.2).

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

At the OLE Day 1 visit or at the visit of the first study drug administration in the Study WN42171, MRI does not have to be repeated if the last MRI performed in the parent studies WN29922 or WN39658 is within 6 months. The MRI can only be used if it was the last prescribed per-protocol MRI in the parent study.

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

Healthy Volunteer Magnetic Resonance Imaging Scans for Site Qualification

In case of a major upgrade to the site's scanner, any other event deemed significant enough to affect image quality, or per central reader guidance, the two volunteers will be asked to complete additional scans that will be reviewed for suitable image quality and used for qualitative comparison. 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. 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 in the context of the two associated PET substudies (a longitudinal amyloid PET substudy and a longitudinal tau PET substudy (see Section 3.1.2).

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

4.5.12 Final Safety and Efficacy Visit Assessments

Participants who complete the treatment period (defined as completion of OLE Week *206* dosing visit) have to complete the final safety and efficacy assessment period 2 weeks following the final dose (Week *208*).

4.5.13 Study Completion or Early Termination Visit Assessments

All participants who withdraw from treatment or discontinue from the study early will be asked to return 2 weeks after the final 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., secondary endpoints) at visits that have efficacy assessments (e.g., OLE Week 52, OLE Week 76, OLE Week 104, *OLE Week 130, OLE Week 156, OLE Week 182, OLE Week 208, and OLE Week 220*).

Autopsy reports, including cause of death, for all participants who die during the study (i.e., prior to the OLE Week *220* follow-up visit) should be requested.

Refer to the schedule of activities to be performed at the study completion (OLE Week *208* or OLE early termination visit) in Appendix 1.

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.

4.5.14 Optional Samples for Research Biosample Repository

4.5.14.1 Overview of the Research Biosample Repository

The RBR is a centrally administered group of facilities used for the long-term storage of human biological specimens, including body fluids, solid tissues, and derivatives thereof (e.g., DNA, RNA, proteins, peptides). The collection, storage, and analysis of RBR samples 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.

Samples for the RBR will be collected from participants who give specific consent to participate in this optional research. RBR samples will be analyzed to achieve one or more of the following objectives:

- To study the association of biomarkers with efficacy or disease progression
- To identify safety biomarkers that are associated with susceptibility to developing adverse events or can lead to improved adverse event monitoring or investigation
- To increase knowledge and understanding of disease biology and drug safety

- 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

4.5.14.2 Approval by the Institutional Review Board or Ethics Committee

Collection, storage, and analysis of RBR samples 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 4.5.14) will not be applicable at that site.

4.5.14.3 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, AD, or drug safety:

- Leftover blood, serum, plasma, CSF samples collected for biomarker analysis, and any derivatives thereof (e.g., DNA, RNA, proteins, peptides)

The above samples may be sent to one or more laboratories for analysis of germline or somatic variants via whole genome sequencing (WGS), whole exome sequencing (WES), or other genomic analysis methods. Genomics is increasingly informing researchers' understanding of disease pathobiology. Whole genome sequencing 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 or new methods for monitoring efficacy and safety or predicting which participants are more likely to respond to a drug or develop adverse events.

Data generated from RBR samples will be analyzed in the context of this study but may also be explored in aggregate with data from other studies. The availability of a larger dataset will assist in identification and characterization of important biomarkers and pathways to support future drug development.

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

RBR samples 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).

4.5.14.4 Confidentiality

RBR samples and associated data will be labeled with a unique patient identification number.

Participant medical information associated with RBR samples 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 samples, 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 samples 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.

4.5.14.5 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 consent 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 samples. 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 samples and data will continue to be used as part of the RBR research.

4.5.14.6 Withdrawal from the Research Biosample Repository

Participants who give consent to provide RBR samples have the right to withdraw their consent at any time for any reason. After withdrawal of consent, any remaining samples will be destroyed or will no longer be linked to the participant. However, if RBR samples have been tested prior to withdrawal of consent, results from those tests will remain as part of the overall research data. If a participant wishes to withdraw consent to the

testing of his or her RBR samples during the study, the investigator must inform the Medical Monitor in writing of the participant's wishes through use of the appropriate RBR Subject Withdrawal Form and must enter the date of withdrawal on the RBR Research Sample Withdrawal of Informed Consent eCRF. If a participant wishes to withdraw consent to the testing of his or her RBR samples after closure of the site, the investigator must inform the Sponsor by emailing the study number and participant number to the following email address:

global.rcr-withdrawal@roche.com

A participant's withdrawal from this study does not, by itself, constitute withdrawal of consent for testing of RBR samples. Likewise, a participant's withdrawal of consent for testing of RBR samples does not constitute withdrawal from this study.

4.5.14.7 Monitoring and Oversight

RBR samples 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 samples 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 TREATMENT, PARTICIPANT, STUDY, AND SITE DISCONTINUATION

4.6.1 Study Treatment Discontinuation

Participants must permanently 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 determination that treatment discontinuation is in the best interest of the participant
- Pregnancy
- Evidence of an intracerebral macrohemorrhage
- Evidence of disseminated leptomeningeal hemosiderosis

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

All participants who withdraw from treatment will be asked to return 2 weeks after their final 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 data (except MRI) and limited efficacy data (i.e., secondary endpoints) at visits that have efficacy assessments (e.g., OLE Week 52, OLE Week 76, OLE Week 104, *OLE Week 130, OLE Week 156, OLE Week 182, OLE Week 208, and OLE Week 220*) according to the schedule of activities.

4.6.2 Participant Discontinuation from the Study

Participants will return to the clinic for an early termination visit 2 weeks after last dose.

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 participant discontinuation from the study may include, but are not limited to, the following:

- Participant withdrawal of consent
- Study termination or site closure
- Adverse event or any medical condition that the investigator or Sponsor determines may jeopardize the participant's safety if he or she continues in the study
- Loss to follow-up
- 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 six consecutive dosing visits because of non–safety-related reasons or more than half of the dosing visits in a calendar year

When participants discontinue early, every effort should be made *to ensure that the safety follow-up period and all related assessments are completed and* to obtain a reason for participant discontinuation from the study. The primary reason for discontinuation from the study should be documented on the appropriate eCRF. If a participant requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Participants who withdraw from the study will not be replaced.

4.6.3 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.

- Data from other studies suggest 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.

4.6.4 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 participating in this study. Eligibility and discontinuation criteria both in the parent studies (WN29922 and WN39658) and in study WN42171 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, severity, and timing of adverse events. In addition, guidelines for managing selected 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 has shown that ARIA events are dose- 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 glucocorticosteroids may be considered.

Rules for management of participants who develop ARIA-E or ARIA-H are provided in Appendix 2.

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 1.3.2.2 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 5.3.5.1 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. Investigators should explain to participants how to recognize the signs and symptoms of hypersensitivity reactions, and participants should be monitored.

5.1.2 Management of Participants Who Experience Adverse Events

5.1.2.1 Dose Modifications and Treatment Interruptions

Participants who completed the double-blind part and did not enter the OLE part of the parent Study (WN29922 or WN39658) will undergo uptitration in this study, which will last at least 34 weeks. During the uptitration phase, participants will undergo brain MRI examinations prior to every dose increase (pre-uptitration MRI scans).
The pre-uptitration MRI scans will determine eligibility for the next uptitration dose, as described in Appendix 2.

In order to determine the radiological severity of an ARIA-E event, the Bioclinica 5-point scale (Bracoud et al. 2017) will be used; refer to Table 2.

Table 2 Bioclinica 5-Point Scale Definition

ARIA-E Extent	ARIA-E Focality	5-Point Scale
No ARIA-E	N/A	0
< 5 cm	Monofocal	1 (Mild)
	Multifocal	2 (Mild +)
5–10 cm	Monofocal	3 (Moderate)
	Multifocal	4 (Moderate +)
> 10 cm	Monofocal	5 (Severe)
	Multifocal	

ARIA-E = amyloid-related imaging abnormality–edema/effusion; N/A = not applicable.

The participants' eligibility for uptitration will be determined according to the ARIA management rules outlined in Appendix 2. In the Study WN42171, there must be a minimum of 3 complete administrations of each dosing level for the participants to be eligible for a pre-uptitration MRI scan. A complete IMP administration is defined as two consecutive dosing visits (one with an odd dose number and one with an even dose number (see Appendix 1 and Table 1). A participant may still be eligible for a pre–uptitration MRI scan and uptitration even if these requirements are not met provided that they have been administered IMP at 3 odd dosing visits at a given dose level (see Table 1).

All participants, regardless of where they completed their gantenerumab dose uptitration (i.e., WN22992 or WN39658 OLE or this study), will undergo regular MRI scans according to the schedule of activities while they are on the target gantenerumab dose.

In addition, the dose adjustment and discontinuation rules for MRI findings as described in Appendix 2 will apply.

The investigator 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 proposed.

The iDMC will review the incidence of ARIA in an unblinded manner and may recommend adjustment of dosing regimen and/or ARIA management rules for the overall study population or for a specific APOE ε4 genotype. *In the event the iDMC which reviews safety in both the parent studies (WN29922 and WN39658) and study WN42171 is no longer required (for instance after the unblinding of the parent studies) evaluation of participant safety may be taken over by the Sponsor's Internal Monitoring Committee (IMC), with details documented in an IMC charter.*

5.2 SAFETY PARAMETERS AND DEFINITIONS

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

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

5.2.1 Adverse Events

According to the ICH guideline for Good Clinical Practice, an adverse event is any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. An adverse event can therefore be any of the following:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product
- Any new disease or exacerbation of an existing disease (a worsening in the character, frequency, or severity of a known condition) (see Sections 5.3.5.10 and 5.3.5.11 for more information)
- 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, or according to National Cancer Institute Common Terminology Criteria for Adverse Events; see Section 5.3.3); the event itself may be of relatively minor medical significance (such as severe headache without any further findings).

Severity and seriousness need to be independently assessed for each adverse event recorded on the eCRF.

Serious adverse events are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions).

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

Adverse events of special interest are required to be reported by the investigator to the Sponsor immediately (i.e., no more than 24 hours after learning of the event; see Section 5.4.2 for reporting instructions). Adverse events of special interest for this study are as follows:

- Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law (see Section 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

Additional data 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 5.3.5.2 for further details on 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 Section 5.4–5.6.
The investigator is also responsible for reporting medical device complaints (see Section 5.4.4).

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

5.3.1 Adverse Event Reporting Period

Investigators will seek information on adverse events at each participant contact.
All adverse events, whether reported by the participant, caregiver, 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:

- All adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study.
- All adverse events occurring after the participant's final visit/last assessment in the parent Study WN29922 or WN39658 will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit/last assessment in Study WN42171 (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 3 provides guidance for assessing adverse event severity.

Table 3 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 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."

5.3.5.2 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 (onset or worsening of CNS symptom[s] attributable to ARIA-E MRI findings in the judgement of the investigator)
- ARIA findings that result in a change in study treatment (e.g., dosage modification, treatment interruption, or treatment discontinuation)
- Findings that are otherwise clinically significant in the investigator's judgment

Any accompanying symptom(s) 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).

5.3.5.3 Diagnosis versus Signs and Symptoms

For adverse events other than ISRs or ARIA (see Sections 5.3.5.1 and 5.3.5.2, respectively), 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.

However, for a serious or severe secondary event such as a fracture following a fall, both events should be reported separately on the eCRF because a fracture is not a typical expected consequence of a fall.

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., ALP and bilirubin $5 \times$ ULN [upper limit of normal] 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 5.3.5.3) 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 solely 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 the parent study and at the beginning of this study. Conditions reported on the General Medical History eCRF in the parent study do not need to be re-entered. They will be reassessed if they are ongoing at the beginning of this study.

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 due to 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
- Planned hospitalization required by the protocol
- Hospitalization for a preexisting condition, provided that all of the following criteria are met:

  The hospitalization was planned prior to the *parent study baseline (WN29922 and WN39658)* 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 Cases of Overdose, Medication Error, Drug Abuse, or Drug Misuse

Overdose (accidental or intentional), medication error, drug abuse, and drug misuse (hereafter collectively referred to as "special situations"), are defined as follows:

- Accidental overdose: accidental administration of a drug in a quantity that is higher than the assigned dose
- Intentional overdose: intentional administration of a drug in a quantity that is higher than the assigned dose
- Medication error: accidental deviation in the administration of a drug
- In some cases, a medication error may be intercepted prior to administration of the drug.
- Drug abuse: intentional excessive use of a drug that may lead to addiction or dependence, physical harm, and/or psychological harm
- Drug misuse: intentional deviation in the administration of a drug that does not qualify as drug abuse

Special situations are not in themselves adverse events but may result in adverse events. Each adverse event associated with a special situation should be recorded separately on the Adverse Event eCRF. If the associated adverse event fulfills seriousness criteria or qualifies as an adverse event of special interest, 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). For gantenerumab $and\ [^{18}F]GTP1$, adverse events associated with special situations should be recorded as described below for each situation:

- Accidental overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the adverse event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the adverse event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the adverse event term. Check the "Accidental overdose" and "Medication error" boxes.
- Drug abuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the adverse event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the adverse event term. Check the "Intentional overdose" and "Drug misuse" boxes.

In addition, all special situations associated with gantenerumab $and\ [^{18}F]GTP1$, regardless of whether they result in an adverse event, should be recorded on the Adverse Event eCRF as described below:

- Accidental overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes.
- Intentional overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" box. If drug abuse is suspected, check the "Drug abuse" box. If drug abuse is not suspected, check the "Drug misuse" box.
- Medication error that does not qualify as an overdose: Enter the name of the drug administered and a description of the error (e.g., wrong dose administered, wrong dosing schedule, incorrect route of administration, wrong drug, expired drug administered) as the event term. Check the "Medication error" box.
- Medication error that qualifies as an overdose: Enter the drug name and "accidental overdose" as the event term. Check the "Accidental overdose" and "Medication error" boxes. Enter a description of the error in the additional case details.

- Intercepted medication error: Enter the drug name and "intercepted medication error" as the event term. Check the "Medication error" box. Enter a description of the error in the additional case details.
- Drug abuse that does not qualify as an overdose: Enter the drug name and "drug abuse" as the event term. Check the "Drug abuse" box.
- Drug abuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug abuse" boxes.
- Drug misuse that does not qualify as an overdose: Enter the drug name and "drug misuse" as the event term. Check the "Drug misuse" box.
- Drug misuse that qualifies as an overdose: Enter the drug name and "intentional overdose" as the event term. Check the "Intentional overdose" and "Drug misuse" boxes.
- Drug administered to someone other than the participant: Enter the drug name and "patient supplied drug to third party" as the event term. Check the "Drug misuse" box.

As an example, an accidental overdose that resulted in a headache would require two entries on the Adverse Event eCRF, one entry to report the accidental overdose and one entry to report the headache. The "Accidental overdose" and "Medication error" boxes would need to be checked for both entries

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.

5.3.5.15 Safety Biomarker Data

Adverse event reports will not be derived from safety biomarker data by the Sponsor, and safety biomarker data will not be included in the formal safety analyses for this study. In addition, safety biomarker data will not inform decisions on participant management.

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

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 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

After informed consent has been obtained:

- All serious adverse events and adverse events of special interest occurring while the participant is in the parent Study (WN29922 or WN39658) will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent Study (WN29922 or WN39658).
- All serious adverse events and adverse events of special interest occurring after the participant's final visit/last assessment in the parent Study (WN29922 or WN39658) will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit/last assessment in Study WN42171 (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 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. 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 through the Informed Consent Form to immediately inform the investigator if they become pregnant during the study or within 16 weeks after the final 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 participant's final visit/last assessment in Study WN42171) 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 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 through use of the reference safety information in the documents listed below:

Drug	Document
Gantenerumab	Gantenerumab Investigator's Brochure
Florbetaben [^{18}F] (Neuraceq™)	Florbetaben [^{18}F] Investigator's Brochure
Flutemetamol [^{18}F] (Vizamyl™)	Flutemetamol [^{18}F] 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 assess the safety, tolerability, and efficacy of long-term administration of open-label gantenerumab in participants with AD who completed Study WN29922 or WN39658.

Data from OLE baseline (see Section 4.5.2 for definition) to the end of study will be summarized. Consequently, where appropriate, data from the parent studies will be combined with data from this protocol.

6.1 DETERMINATION OF SAMPLE SIZE

The sample size will include all eligible participants who consent to this study.
The sample size is expected to be no more than approximately 2032 participants but will be determined by the number of participants who complete parent Studies (WN29922 and WN39658) and enroll in this study.

6.2 SUMMARIES OF CONDUCT OF STUDY

Enrollment, participant disposition, and incidence of protocol deviations will be summarized using descriptive statistics for all enrolled participants.

6.3 SUMMARIES OF DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic and baseline characteristics (such as age, sex, race, disease stage, *APOE* ε4 status, and use and non-use of background therapy for AD) will be summarized descriptively for all enrolled participants.

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 SAFETY ANALYSES

The safety analysis population will include all enrolled participants who received at least one dose of study drug in this protocol.

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

- Nature, frequency, severity, timing, and outcomes of adverse events and serious adverse events
- Physical examinations (including neurological systems), vital signs, ECG, laboratory tests, and C-SSRS
- Nature, frequency, severity, and timing of ARIA-E and ARIA-H
- Nature, frequency, severity, timing, and outcomes of injection-site reactions
- Incidence of treatment discontinuations for adverse events
- Incidence of adverse events of special interest

Statistical methods, endpoint definitions, and analyses of the safety endpoints will be described in a SAP.

6.5 EFFICACY ANALYSES

The secondary and exploratory efficacy analyses will use all enrolled participants to investigate both the long-term efficacy and potential disease modifying effect of long-term gantenerumab. Associated estimands, including those pertaining to a delayed start analysis, will be described in detail in a Statistical Analysis Plan (SAP).
The efficacy endpoints collected during both the double-blind and OLE parts of the parent Study (WN29922 or WN39658) may be combined with data from this study in order to evaluate the long-term effect of gantenerumab.

6.6 PHARMACOKINETIC ANALYSES

Plasma concentration data for gantenerumab will be tabulated and summarized. Descriptive summary statistics will include the arithmetic mean, median, range, standard deviation, 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 analyze 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 area under the concentration–time curve, maximum plasma concentration observed (C_{max}), and trough plasma concentration, will depend on the final PK model used for this analysis. The results of this modeling analysis may be reported separately from the clinical study report. Cerebrospinal fluid concentrations of gantenerumab may be tabulated and summarized as appropriate.

Prior to the completion of the study, one or more separate cutoff date(s) for PK samples may be established to allow expedient sample analyses and early access by third party vendors.

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

6.7 IMMUNOGENICITY ANALYSES

The immunogenicity analysis population will consist of all participants with at least one ADA assessment. The numbers and proportions of ADA-positive participants and ADA-negative participants prior to OLE drug administration and after OLE drug administration will be summarized using descriptive statistics.

Prior to completion of the study, one or more separate cutoff date(s) for ADA samples may be established to allow expedient samples analyses and early access by third party vendors.

6.8 BIOMARKER ANALYSES

Exploratory PD and biomarker endpoints will be analyzed using descriptive statistics, subgroup analysis, or statistical models if appropriate. For longitudinally measured

endpoints, the change from baseline will be estimated if appropriate. Prior to the completion of the study, one or more separate cutoff date(s) for PD biomarker samples may be established to allow expedient sample analyses and early access by third party vendors. Exploratory biomarkers may be reported separately.

6.9 HEALTH STATUS UTILITY ANALYSES

Change over time in EQ-5D health utility index-based will be calculated. EQ-5D will be summarized using descriptive statistics. Details will be provided in a SAP. EQ-5D will be used to estimate health state utility values needed for economic modeling. Such analyses will be reported separately.

6.10 INTERIM ANALYSES

To adapt to information that may emerge during the course of this study, the Sponsor may choose to conduct one or more interim analysis(es) which may include efficacy, safety and biomarker outcomes. An interim analysis may be considered when the parent pivotal Studies WN29922 and WN39658 are completed and the submission folder is under preparation. Details will be pre-specified in a 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 (see Section 7.3 for details). 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. Food and Drug Administration (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

The 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. The 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. The 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 that must be kept with the study records. Acknowledgement of receipt of the data is required.

7.3 ELECTRONIC REPORTED OUTCOME DATA

An electronic device will be used by participants, caregivers, and appropriate site staff to capture COA data. The device is designed for entry of data in a way that is attributable, secure, and accurate, in compliance with FDA regulations for electronic records (21 CFR Part 11). The data will be transmitted to a centralized database maintained by the electronic device vendor.

The electronic data will be available for view access only, via a secure online web portal. Only identified and trained users may view the data, and their actions will 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.

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 that must be kept with the study records as source data. Acknowledgement of receipt of the data is required. In addition, the Sponsor will receive all data in a machine-readable format.

7.4 SOURCE DATA DOCUMENTATION

Study monitors will perform ongoing source data verification and review 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 and review, 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 or paper COA data, Informed Consent Forms, laboratory test results, and medication inventory records, must be retained by the Principal Investigator for 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.

Roche will retain study data for 25 years after the final study results have been reported or for the length of time required by relevant national or local health authorities, whichever is longer.

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 applicable 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) and applicable local, regional, and national laws.

8.2 INFORMED CONSENT

The Sponsor's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as an Assent Form or Mobile 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.

If the Consent Forms are revised (through an amendment or an addendum) while a participant is participating in the study, the participant or a legally authorized representative must re-consent by signing the most current version of the Consent Forms or the addendum, in accordance with applicable laws and IRB/EC policy. For any updated or revised Consent Forms, the case history or clinical records for each 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 9.7).

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 patient 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.

Given the complexity and exploratory nature of exploratory biomarker analyses, 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 (see Section 9.6).

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.

Study data may be submitted to government or other health research databases or shared with researchers, government agencies, companies, or other groups that are not participating in this study. These data may be combined with or linked to other data and used for research purposes, to advance science and public health, or for analysis, development, and commercialization of products to treat and diagnose disease. In addition, redacted Clinical Study Reports and other summary reports will be provided upon request (see Section 9.6).

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 (see definition of end of study in Section 3.2).

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 MANAGEMENT OF STUDY QUALITY

The Sponsor will implement a system to manage the quality of the study, focusing on processes and data that are essential to ensuring participant safety and data integrity. Prior to study initiation, the Sponsor will identify potential risks associated with critical trial processes and data and will implement plans for evaluating and controlling these risks. Risk evaluation and control will include the selection of risk-based parameters (e.g., adverse event rate, protocol deviation rate) and the establishment of quality tolerance limits for these parameters. Detection of deviations from quality tolerance limits will trigger an evaluation to determine if action is needed. Details on the establishment and monitoring of quality tolerance limits will be provided in a Quality Tolerance Limit Management Plan.

9.4 SITE INSPECTIONS

Site visits will be conducted by the Sponsor or an authorized representative for inspection of study data, participants' 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.

9.5 ADMINISTRATIVE STRUCTURE

The overall procedures for quality assurance of clinical study data are described in Roche standard operating procedures. This study will be sponsored by F. Hoffmann-La

Roche Ltd. The Sponsor 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.

9.6 DISSEMINATION 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, at scientific congresses, in clinical trial registries, and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results. Study data may be shared with others who are not participating in this study (see Section 8.4 for details), and redacted Clinical Study Reports and other summary reports will be made available upon request. For more information, refer to the Roche Global Policy on Sharing of Clinical Study Information at the following website:

https://www.roche.com/innovation/process/clinical-trials/data-sharing/

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.

9.7 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 Schedule of Activities for Participants Who Did Not Participate in the OLE Part of Parent Study WN29922 or WN39658

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Informed consent(s)	x																				
Review of inclusion and exclusion criteria	x	B																			
Medical history, personal status, and demographic data	x																				
Weight and height [e]		x													x						x
Clinical RNA samples		x [b]																			x
Urinalysis		x [r]																			
Coagulation (PT)		B [b]																			
12-Lead ECG		B [b]																			x
Plasma PK sample [f]		B	x												*B*						x
Plasma ADA sample		B													*B*						x

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Serum chemistry [g] and hematology [h]		B [b]													x						x
Plasma biomarker sample		x [b]													x						x
Complete physical examination (includes neurologic systems) [i]		B[b]																			x
Limited physical examination [j]															x						x
MRI scan [k]		B [b, l]							B						B						x
CSF and matching serum samples [m]		x [b]																			
CDR		P& CG [b]													P& CG						P& CG
ADAS-Cog13		P [b]													P						P
Verbal Fluency Task		P [b]													P						P
Coding		P [b]													P						P

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
ADCS-ADL		CG [b]													CG						CG
FAQ		CG [b]													CG						CG
MMSE		P [b]													P						P
EQ-5D		CG [b]													CG						CG
QoL-AD		P& CG [b]													P& CG						P& CG
ZCI-AD		CG [b]													CG						CG
RUD-Lite		CG [b]													CG						CG
NPI-Q		CG [b]													CG						CG
C-SSRS SLV		P [b]													P						P
Vital signs [n]		B	x	B	B	B	B	B	B	B	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	x	x	x	x	x	x	x	x	x
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B		B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	B	

Appendix 1: Schedule of Activities

Assessment/Procedure	Screening	BL		OLE (week)																	UV[a]
	Including While in parent study to −1 Day	OLE Day 1	OLE Day 4	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	
Dose number in the Study WN42171		1 [b]		2	3	4	5	6	7	8	9 [c]	10 [c]	11 [c]	12 [c]	13 [d]	14 [c]	15 [c]	16 [c]	17 [c]	18 [c]	
Dose level for participants previously on active		510 mg Q2W																			
Dose level for participants previously on placebo		120 mg							255 mg						510 mg						
Study drug administration [q]		x		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	

Appendix 1: Schedule of Activities

Aβ = amyloid beta; ADA = anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; BL = baseline; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF=electronic Case Report Form; EQ-5D = EuroQol 5-Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; SLV = since last visit; T4 = thyroxine; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion; P = participant completion; P&CG = participant and caregiver completion.

Notes: The participant, the site, and the Sponsor will be kept blinded to the dose level given in order to keep the previous treatment assignment blinded. The visit window is ±3 days and +3 days for OLE non-dosing Day 4. It is recommended that not more than 2 dosing visits are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per baseline visit (OLE Day 1) for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry, and hematology; complete physical examination) performed within 4 weeks prior to Day 1 may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed *at final efficacy and safety visit of the parent study and* within 6 months prior to OLE Day 1. *MRI must have been performed after the last dose in the parent study.* If a clinical RNA sample or plasma biomarker or CSF and matching serum sample (where applicable) was collected at the final efficacy and safety visit of the parent study, another one does not have to be collected.

[c] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[d] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. 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, 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.

[e] Height will be assessed only at the first dosing visit in Study WN42171.

[f] 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 practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA–E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). 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 a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI should 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.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in Studies WN29922 or WN39658 based on CSF Aβ and tau level results. It 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 (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. 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.

[o] After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658, all adverse events will be reported on the WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[p] 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.

[q] 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 SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 2 hours after the first 8 dosing visits. From the ninth dose, 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.

[r] If deemed necessary by the investigator, urinalysis may 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.

Table 2 Schedule of Activities for Participants Who Have Completed Uptitration in Study WN42171 (continuation of Table 1)

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
Weight						x		x			x	x
Clinical RNA samples											x	x
12-Lead ECG											x	x
Plasma PK sample [d]				x (Site visit)		B		B		x (Site visit)	x	x
Plasma ADA sample						*B*		B			x	x
Serum chemistry [e] and hematology [f]						x		x			x	x
Plasma biomarker sample						x					x	x
Complete physical examination (includes neurologic systems) [g]											x	x
Limited physical examination [h]	B					B		B				x
MRI scan [i]	B				B W48 [j]			B			x [j]	x

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
CSF and matching serum samples [k]						x					x	
CDR						P&CG		P&CG			P&CG	P&CG
ADAS-Cog13						P		P			P	P
Verbal Fluency Task						P		P			P	P
Coding						P		P			P	P
ADCS-ADL						CG		CG			CG	CG
FAQ						CG		CG			CG	CG
MMSE						P		P			P	P
EQ-5D						CG		CG			CG	CG
QoL-AD						P&CG		P&CG			P&CG	P&CG
ZCI-AD						CG		CG			CG	CG
RUD-Lite						CG		CG			CG	CG
NPI-Q						CG		CG			CG	CG

Appendix 1: Schedule of Activities

Assessment/Procedure	Treatment Period										Early Term Visit [c]	UV [a]
	OLE (week)											
Study schedule	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171	19	20	21		22–26	27	28–38	39	40–52			
Dose level in milligrams (mg)	510 Q2W											
C-SSRS SLV						P		P			P	P
Vital signs [l]	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
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [n]	B	B	B		B	B	B	B	B		x	x
Study drug administration [o]	x	x	x		x	x	x	x	x			

Appendix 1: Schedule of Activities

Aβ = amyloid beta; ADA = anti-drug antibody; ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer's Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; Assess = assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF = electronic Case report Form; EQ-5D = EuroQol-5 Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; OLE = open-label extension; PK = pharmacokinetic; Q2W = every 2 weeks; QoL-AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; T4 = thyroxine; Term = termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion; P = participant completion; P&CG = participant and caregiver completion.

Notes: The visit window is ± 3 days. It is recommended that not more than 2 doses are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule for subsequent visits.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. 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, 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.

[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 practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[e] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). 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 a meal.

[f] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[g] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[h] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[i] MRI should 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 will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It 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 (if applicable).

[l] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. 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] After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[n] 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.

[o] 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 SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

Table 3 Schedule of Activities for Participants Who Have Completed the OLE Part of Parent Study WN29922 or WN39658

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
Informed consent(s)	x												
Review of inclusion and exclusion criteria	x	B [e]											
Medical history, personal status, and demographics	x												
Weight and height [d]		x [e]					x		x			x	x
Clinical RNA samples												x	x
Urinalysis		x [r]											
Coagulation (PT)		B [e]											
12-Lead ECG		B [e]										x	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
Plasma PK sample [f]		B			x (Site visit)		B		B		x (Site visit)	x	x
Plasma ADA sample		B					*B*		B			x	x
Serum chemistry [g] and hematology [h]		B [e]					x		x			x	x
Plasma biomarker sample							x					x	x
Complete physical examination (includes neurologic systems) [i]												x	x
Limited physical examination [j]		B [e]					B		B				x
MRI scan [k]		B [e, l]				B W48 [l]			B			x [i]	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
CSF and matching serum samples [m]							*x*					x	
CDR		P&CG [e]					P&CG		P&CG			P&CG	P&CG
ADAS-Cog13		P [e]					P		P			P	P
Verbal Fluency Task		P [e]					P		P			P	P
Coding		P [e]					P		P			P	P
ADCS-ADL		CG [e]					CG		CG			CG	CG
FAQ		CG [e]					CG		CG			CG	CG
MMSE		P [e]					P		P			P	P
EQ-5D		CG [e]					CG		CG			CG	CG
QoL-AD		P&CG [e]					P&CG		P&CG			P&CG	P&CG
ZCI-AD		CG [e]					CG		CG			CG	CG

Appendix 1: Schedule of Activities

Assessment/ Procedure	Screening	Treatment Period										Early Term. Visit [c]	UV [a]
		OLE (week)											
Study schedule	Including while in parent study to − 1 day before first dosing visit	36	38 [b]	40 [b]	41	42–50 [b]	52 [c]	54–74 [b]	76 [c]	78–102 [b]	103		
Dose number in the Study WN42171		1	2	3		4–8	9	10–20	21	22–34			
Dose level in milligrams (mg)		510 Q2W											
RUD-Lite		CG [e]					CG		CG			CG	CG
NPI-Q		CG [e]					*CG*		CG			CG	CG
C-SSRS SLV		P [e]					P		P			P	P
Vital signs [n]		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
Adverse events [o]	x	x	x	x	x	x	x	x	x	x	x	x	x
Urine pregnancy test [p]		B	B	B		B	B	B	B	B		x	x
Study drug administration [q]		x	x	x		x	x	x	x	x			

Appendix 1: Schedule of Activities

ADAS-Cog13 = Alzheimer's Disease Assessment Scale–Cognition, Subscale 13; ADCS-ADL = Alzheimer Disease Cooperative Study Group–Activities of Daily Living; ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; assess = assessment; CDR = Clinical Dementia Rating; CSF = cerebrospinal fluid; C-SSRS = Columbia–Suicide Severity Rating Scale; DTI = diffusion tensor imaging; eCRF = electronic Case Report Form; EQ-5D = EuroQol-Five Dimensions; FAQ = Functional Activities Questionnaire; FU = follow-up; MMSE = Mini-Mental State Examination; MRI = magnetic resonance imaging; NPI-Q = Neuropsychiatric Inventory Questionnaire; PK = pharmacokinetic; Q2W = every 2 weeks; QoL–AD = Quality of Life–Alzheimer's Disease; RUD-Lite = Resource Utilization in Dementia–Lite; term = termination; UV = unscheduled visit; ZCI-AD = Zarit Caregiver Interview for Alzheimer's Disease.

B = before study drug administration; CG = caregiver completion P = participant completion; P&CG = participant and caregiver completion.

Notes: The visit window is ± 3 days and + 3 days for OLE non-dosing Day 4. It is recommended that not more than 2 administrations are given (i.e., 2 × 510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

For participants for whom the uptitration in the parent study took longer than 34 weeks to complete, the first visit in Study WN42171 will be adapted according to the schedule of the visits they had in the parent study.

[a] The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.

[b] At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.

[c] Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. 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, 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.

[d] Height will be assessed only at the first dosing visit in Study WN42171.

[e] Only for participants who participated in the OLE part of the parent study who are rolling over to this study: Results of standard-of-care tests or examinations (coagulation, ECG, serum chemistry and hematology, complete physical examination) performed in the parent studies within 4 weeks prior to the visit may be used. MRI, C-SSRS, and cognitive scale results may be used if they have been performed within 6 months prior to *the first dosing visit*. MRI must have been performed after the last dose in the parent study.

[f] 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 practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).

[g] Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). 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 a meal.

[h] Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).

[i] A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.

[j] Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.

[k] MRI should 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.

[l] Includes resting-state functional MRI and DTI outcome measures, where available.

[m] Lumbar puncture will be performed only in participants who were randomized in Studies WN29922 or WN39658 based on CSF Aβ and tau level results. It 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 (if applicable).

[n] Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. 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.

[o] After informed consent has been obtained, all adverse events occurring while the participant is in the parent study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).

[p] 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.

[q] 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 SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.

[r] If deemed necessary by the investigator, urinalysis may 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.

Table 4 Schedule of Activities for Participants Who Have Completed Uptitration in Study WN42171 (2-year extension)

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*53*	*54–65*	*66*	*67–78*	*79*	*80–91*	*92*	*93–103*	*104*				
Dose level in milligrams (mg)	*510 Q2W*												
Weight	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*
Clinical RNA samples	*x*									*x*		*x*	*x*
12-lead ECG	*x*										*x*	*x*	*x*
Coagulation (PT)	*B*												
Plasma PK sample [d]					*B*					*x*	*x*	*x*	*x*
Plasma ADA sample	*B*				*B*					*x*	*x*	*x*	*x*
Serum chemistry [e] *and hematology* [f]	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158—180 [b]	182 [c]	184—204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	53	54–65	66	67–78	79	80–91	92	93–103	104				
Dose level in milligrams (mg)	510 Q2W												
Plasma biomarker sample	x				x					x		x	x
Complete physical examination (includes neurologic systems) [g]	B									x		x	x
Limited physical examination [h]			B		B		B						x
MRI scan [i]	B [j]		B		B [j]		B			x [j]		x [j]	x
CSF and matching serum samples [k]	x				x					x		x	
CDR	P&CG		P&CG		P&CG		P&CG			P&CG		P&CG	P&CG
ADAS-Cog13	P		P		P		P			P		P	P
Verbal Fluency Task	P		P		P		P			P		P	P

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158—180 [b]	182 [c]	184—204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	53	54–65	66	67–78	79	80–91	92	93–103	104				
Dose level in milligrams (mg)	510 Q2W												
Coding	P		P		P		P			P		P	P
ADCS-ADL	CG		CG		CG		CG			CG		CG	CG
FAQ	CG		CG		CG		CG			CG		CG	CG
MMSE	P		P		P		P			P		P	P
EQ-5D	CG				CG					CG		CG	CG
QoL-AD	P&CG				P&CG					P&CG		P&CG	P&CG
ZCI-AD	CG				CG					CG		CG	CG
RUD-Lite	CG				CG					CG		CG	CG
NPI-Q	CG				CG					CG		CG	CG
C-SSRS SLV	P		P		P		P			P		P	P
Vital signs [l]	B	B	B	B	B	B	B	B	B	x	x	x	x
Concomitant medications	x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events [m]	x	x	x	x	x	x	x	x	x	x	x	x	x

Appendix 1: Schedule of Activities

Assessment/ Procedure	Treatment Period									Final Safety and Efficacy Assessment	Follow-Up Period	Early Term. Visit	UV [a]
	OLE (week)												
Study schedule	104 [c]	106–128 [b]	130 [c]	132–154 [b]	156 [c]	158–180 [b]	182 [c]	184–204 [b]	206 [b]	208 [c]	220		
Dose number in Study WN42171	53	54–65	66	67–78	79	80–91	92	93–103	104				
Dose level in milligrams (mg)	510 Q2W												
Urine pregnancy test [n]	B	B	B	B	B	B	B	B	B	x	x	x	x
Study drug administration [o]	x	x	x	x	x	x	x	x	x				

Aβ =amyloid beta; ADA =anti-drug antibody; ADAS-Cog13 =Alzheimer's Disease Assessment Scale−Cognition, Subscale 13; ADCS-ADL =Alzheimer's Disease Cooperative Study Group−Activities of Daily Living; ARIA-E =amyloid-related imaging abnormality−edema/effusion; ARIA-H =amyloid-related imaging abnormality−microhemorrhage/hemosiderin deposition; Assess =assessment; B = before study drug administration; CDR =Clinical Dementia Rating; CG =caregiver completion; CSF =cerebrospinal fluid; C-SSRS =Columbia−Suicide Severity Rating Scale; DTI =diffusion tensor imaging; eCRF =electronic Case report Form; EQ-5D = EuroQol-5 Dimension Questionnaire; FAQ = Functional Activities Questionnaire; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory Questionnaire; OLE =open-label extension; P&CG =participant and caregiver completion; P =participant completion; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life−Alzheimer's Disease; RUD-Lite =Resource Utilization in Dementia−Lite; T4 =thyroxine; Term =termination; UV =unscheduled visit; ZCI-AD =Zarit Caregiver Interview for Alzheimer's Disease.

Notes: The visit window is ±3 days. It is recommended that not more than 2 doses are given (i.e., 2 ×510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] *The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.*

[b] *At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.*

[c] *Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. 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, 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.*

[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 practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).*

[e] *Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). 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 a meal.*

[f] *Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).*

[g] *A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[h] *Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.*

[i] *MRI should 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 will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It 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 (if applicable).*

[l] *Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. 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] *After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).*

[n] *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.*

[o] *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 SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.*

Table 5 Schedule of Activities for Participants Who Have Completed the OLE Part of Parent Study WN29922 or WN39658 (2-Year Extension)

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*35*	*36–47*	*48*	*49–60*	*61*	*62–73*	*74*	*75–85*	*86*				
Dose level in milligrams (mg)	*510 Q2W*												
Weight	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*
Clinical RNA samples	*x*									*x*		*x*	*x*
12-lead ECG	*x*										*x*	*x*	*x*
Coagulation (PT)	*B*												
Plasma PK sample [d]					*B*					*x*	*x*	*x*	*x*
Plasma ADA sample	*B*				*B*					*x*	*x*	*x*	*x*
Serum chemistry [e] *and hematology* [f]	*x*		*x*		*x*		*x*			*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*35*	*36–47*	*48*	*49–60*	*61*	*62–73*	*74*	*75–85*	*86*				
Dose level in milligrams (mg)	*510 Q2W*												
Plasma biomarker sample	*x*				*x*					*x*		*x*	*x*
Complete physical examination (includes neurologic systems) [g]	*B*									*x*		*x*	*x*
Limited physical examination [h]			*B*		*B*		*B*						*x*
MRI scan [i]	*B* [j]		*B*		*B* [j]		*B*			*x* [j]		*x* [j]	*x*
CSF and matching serum samples [k]	*x*				*x*					*x*		*x*	
CDR	*P&CG*		*P&CG*		*P&CG*		*P&CG*			*P&CG*		*P&CG*	*P&CG*
ADAS-Cog13	*P*		*P*		*P*		*P*			*P*		*P*	*P*

Appendix 1: Schedule of Activities

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*35*	*36–47*	*48*	*49–60*	*61*	*62–73*	*74*	*75–85*	*86*				
Dose level in milligrams (mg)	*510 Q2W*												
Verbal Fluency Task	*P*		*P*		*P*		*P*			*P*		*P*	*P*
Coding	*P*		*P*		*P*		*P*			*P*		*P*	*P*
ADCS-ADL	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
FAQ	*CG*		*CG*		*CG*		*CG*			*CG*		*CG*	*CG*
MMSE	*P*		*P*		*P*		*P*			*P*		*P*	*P*
EQ-5D	*CG*				*CG*					*CG*		*CG*	*CG*
QoL-AD	*P&CG*				*P&CG*					*P&CG*		*P&CG*	*P&CG*
ZCI-AD	*CG*				*CG*					*CG*		*CG*	*CG*
RUD-Lite	*CG*				*CG*					*CG*		*CG*	*CG*
NPI-Q	*CG*				*CG*					*CG*		*CG*	*CG*
C-SSRS SLV	*P*		*P*		*P*		*P*			*P*		*P*	*P*
Vital signs [l]	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*x*	*x*	*x*	*x*

Appendix 1: Schedule of Activities

Assessment/ Procedure	*Treatment Period*									*Final Safety and Efficacy Assessment*	*Follow-Up Period*	*Early Term. Visit*	*UV* [a]
	OLE (week)												
Study schedule	*104* [c]	*106–128* [b]	*130* [c]	*132–154* [b]	*156* [c]	*158—180* [b]	*182* [c]	*184—204* [b]	*206* [b]	*208* [c]	*220*		
Dose number in Study WN42171	*35*	*36–47*	*48*	*49–60*	*61*	*62–73*	*74*	*75–85*	*86*				
Dose level in milligrams (mg)	*510 Q2W*												
Concomitant medications	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Adverse events [m]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*
Urine pregnancy test [n]	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*B*	*x*	*x*	*x*	*x*
Study drug administration [o]	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*	*x*				

Aβ =amyloid beta; ADA =anti-drug antibody; ADAS-Cog13 =Alzheimer's Disease Assessment Scale−Cognition, Subscale 13; ADCS-ADL =Alzheimer's Disease Cooperative Study Group−Activities of Daily Living; ARIA-E =amyloid-related imaging abnormality−edema/effusion; ARIA-H =amyloid-related imaging abnormality−microhemorrhage/hemosiderin deposition; Assess =assessment; B =before study drug administration; CDR =Clinical Dementia Rating; CG =caregiver completion; CSF =cerebrospinal fluid; C-SSRS =Columbia−Suicide Severity Rating Scale; DTI =diffusion tensor imaging; eCRF =electronic Case report Form; EQ-5D =EuroQol-5 Dimension Questionnaire; FAQ =Functional Activities Questionnaire; MMSE =Mini-Mental State Examination; MRI =magnetic resonance imaging; NPI-Q =Neuropsychiatric Inventory Questionnaire; OLE =open-label extension; P&CG =participant and caregiver completion; P =participant completion; PK =pharmacokinetic; Q2W =every 2 weeks; QoL-AD =Quality of Life−Alzheimer's Disease; RUD-Lite =Resource Utilization in Dementia−Lite; T4 =thyroxine; Term =termination; UV =unscheduled visit; ZCI-AD =Zarit Caregiver Interview for Alzheimer's Disease.

Notes: The visit window is ±3 days. It is recommended that not more than 2 doses are given (i.e., 2 ×510 mg Q2W) within 28 days. Participants should return to initial planned schedule per randomization for subsequent visits.

[a] *The relevant assessments will be determined by the Principal Investigator per clinical judgment, not necessary to include all assessments listed above. An additional plasma and RNA blood sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E); following new or worsened ARIA-E.*

[b] *At applicable sites, administration of gantenerumab may be performed by a mobile nursing professional at the participant's home or another suitable location, such as a nursing center, to improve access and convenience for participants participating in the study.*

[c] *Visit may be split over 2 consecutive days. All cognitive and functional assessments should be completed first. 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, 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.*

[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 practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).*

[e] *Serum chemistry includes AST, ALT, ALP, total protein, total bilirubin, serum albumin, creatine phosphokinase, sodium, potassium, calcium, BUN, and serum creatinine (and creatinine clearance calculated by the central laboratory). 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 a meal.*

[f] *Hematology includes WBC count, RBC count (with morphology), hemoglobin, hematocrit, platelet count, and differential count (neutrophils, eosinophils, basophils, monocytes, lymphocytes, other cells).*

[g] *A complete physical examination, performed at specified visits, should include an evaluation of the head, eyes, ears, nose, and throat, and the cardiovascular, dermatologic, musculoskeletal, respiratory, gastrointestinal, and neurologic systems; genitourinary examinations may be performed if clinically indicated.*

[h] *Limited, symptom-directed physical examinations; changes from baseline abnormalities should be recorded in participant notes.*

[i] *MRI should 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 will be performed only in participants who were randomized in the WN29922 or WN39658 studies based on CSF Aβ and tau level results. It 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 (if applicable).*

[l] *Vital signs include measurements of pulse rate, respiratory rate, systolic and diastolic blood pressure while the participant is in a seated position, and temperature. 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] *After informed consent has been obtained, all adverse events occurring while the participant is in the parent Study WN29922 or WN39658 will be reported on the parent Adverse Event eCRF until the participant's final visit/last assessment in the parent study. After the participant's final visit/last assessment in the parent Study WN29922 or WN39658 all adverse events will be reported on the Study WN42171 Adverse Event eCRF until the participant's final visit (including long-term follow-up visits).*

[n] *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.*

[o] *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 SC injection (full details are provided in the pharmacy manual). Participants should be observed for at least 1 hour after dosing. Study personnel preparing and administering study drug must not be involved with any efficacy assessments or safety evaluations.*

Appendix 2 Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristic	Action to Be Taken
ARIA-E	Asymptomatic and mild (Bioclinica severity 1)	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Then, resume the standard MRI schedule.
	Asymptomatic and mild+ (Bioclinica severity 2) or moderate (Bioclinica severity 3)	**During uptitration period:** • Continue study drug at the same dose level and do not uptitrate. • Perform MRI scans at 4-week intervals until ARIA-E resolves. • Once ARIA-E resolves, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Continue study drug according to the schedule of administration. • Perform MRI scans at 4-week intervals until ARIA-E resolves. Then, resume the standard MRI schedule.
	Asymptomatic and moderate+ (Bioclinica severity 4) or severe (Bioclinica severity 5) Or Symptomatic ARIA-E [a] of any severity (Bioclinica severity 1–5)	**During uptitration period:** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug at the dose level given at the time the event was detected. • Perform an MRI scan after two consecutive dosing visits. • If no new ARIA-E is detected, continue uptitration and resume the standard MRI schedule. **During treatment period (at target dose):** • Temporarily interrupt study drug. • Perform MRI scans at 4-week intervals until ARIA-E (and any ARIA-E symptom/s) resolves. • Once ARIA-E (and any ARIA-E symptom/s) resolves, reintroduce study drug. • Perform an MRI scan after two consecutive dosing visits. • If no new ARIA-E is detected, resume the standard MRI schedule.
	Any recurrence of ARIA-E	• Treat as above.

Appendix 2: Management Rules for Amyloid-Related Imaging Abnormalities

Event	Characteristic	Action to Be Taken
ARIA-H	Without disseminated LH	• Continue study drug according to the schedule of administration (including uptitration). • Perform MRI scans according to the standard MRI schedule.
	Disseminated LH	• Permanently discontinue study drug.

ARIA-E = amyloid-related imaging abnormality–edema/effusion; ARIA-H = amyloid-related imaging abnormality–microhemorrhage/hemosiderin deposition; LH = leptomeningeal hemosiderosis; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q4W = every 4 weeks.

Notes:

- Disseminated LH is defined as more than three focal leptomeningeal hemosiderosis cumulatively.
- If ARIA-E and disseminated LH co-occur, the more conservative management rule will apply.
- The investigator may choose to perform additional MRI monitoring for ARIA at any time.
- In exceptional cases of 1) an ARIA-E that is asymptomatic with Bioclinica severity 1 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, gantenerumab can be either reintroduced or uptitrated, as applicable, and Q4W MRI monitoring may no longer be necessary, as determined by the Sponsor and investigator.
- A PK sample will be obtained as soon as soon as practicable (e.g., at an unscheduled visit or the next study visit) following a MRI scan showing new occurrence or worsening of ARIA-E or ARIA-H that meets the discontinuation criteria (e.g., during an unscheduled visit).
- An additional plasma and RNA sample for the assessment of exploratory biomarkers will be obtained as soon as practicable (e.g., at an unscheduled visit or the next study visit) following each MRI scan showing ARIA-E until and including ARIA-E resolution (i.e., new, worsened, stable, improved, resolved ARIA-E).

[a] Symptomatic ARIA-E is defined as onset or worsening of CNS symptom(s) that is/are attributable to ARIA-E MRI findings in the judgement of the Principal Investigator or appropriately medically qualified subinvestigator.

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